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Application Number	08/765,108
Filing Date	March 27, 1997
First Named Inventor	Monty Kreiger
Art Unit	1646
Examiner Name	John Ulm
Attorney Docket Number	MIT 6620 CIP

Total Number of Pages in This Submission

ENCLOSURES *(Check all that apply)*

- [x] Fee Transmittal Form
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- [ ] Amendment/Reply
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SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual name	Patrea L. Pabst, Esq., Reg. No. 31,284 Holland & Knight LLP Suite 2000, One Atlantic Center; 1201 West Peachtree Street, N.E.; Atlanta, GA 30309-3400
Signature	
Date	February 6, 2004

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FEE TRANSMITTAL for FY 2004

Effective 10/01/2003. Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 330.00

Complete if Known	
Application Number	08/765,108
Filing Date	March 27, 1997
First Named Inventor	Monty Krieger
Examiner Name	John Ulm
Art Unit	1646
Attorney Docket No.	MIT 6620 CIP

METHOD OF PAYMENT *(check all that apply)*

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FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) ($)

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

	Extra Claims		Fee from below	Fee Paid
Total Claims		-20* =		X =
Independent Claims		-3** =		X =
Multiple Dependent				=

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

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FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	330.00
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37 CFR 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify) _____

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SUBTOTAL (3) ($) 330.00

SUBMITTED BY				(Complete *(if applicable)*)	
Name (Print/Type)	Patrea L. Pabst	*Registration No. (Attorney/Agent)*	31,284	*Telephone*	(404) 817-8473
Signature				*Date*	February 6, 2004

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants: Monty Krieger and Susan L. Acton

Serial No.: 08/765,108 Art Unit: 1646

Filed: March 27, 1997 Examiner: Michael T. Brannock

For: *CLASS BI AND CI SCAVENGER RECEPTORS*

Mail Stop Appeal Brief - Patents
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APPEAL BRIEF

Sir:

This is an appeal from the rejection of claims 11-13, 19-22 and 44-50 in the Office Action mailed August 6, 2003, in the above-identified patent application. A Notice of Appeal was mailed on December 8, 2003. A check in the amount of $330.00 for the filing of this Appeal Brief for a large entity is also enclosed.

It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-1868.

(1) REAL PARTY IN INTEREST

The real party in interest of this application is , the assignee Massachusetts Institute of Technology, Cambridge, Massachusetts.

(2) RELATED APPEALS AND INTERFERENCES

This is application was previously before the Board of Appeals as appeal number 2001-1495, remanded to the examiner in the decision dated September 25, 2001. There is one other related appeal known to appellant, the undersigned, or appellant's assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal, the appeal in the parent application, U.S. Serial No. 08/265,428 entitled "Class BI and CI Scavenger Receptors" filed June 23, 1994 by Monty Krieger and Susan Acton.

Please note that the inventorship of this application was amended in the Preliminary Amendment mailed December 23, 1996, cancelling claims 1-8 and 23-43, since Atillio Rigotti is not an inventor of the remaining claims. The inventorship was clarified by the Examiner in the Office Action mailed March 5, 2002 on page 3.

(3) STATUS OF CLAIMS ON APPEAL

Claims 11-15, 19-22, and 44-50 are pending. Claims 14 and 15 are allowable. Claims 1-8 and 23-43 were cancelled in the Amendment mailed December 23, 1996. Claims 9 and 10 were cancelled in an Amendment mailed February 11, 1999. Claims 16-18 were cancelled in an Amendment mailed December 29, 1997. Claims 11-13, 19-22 and 44-50 are on appeal. The text of each claim on appeal, as pending, is set forth in an Appendix to this Appeal Brief.

(4) STATUS OF AMENDMENTS

The claims were last amended in the amendment mailed February 10, 2003.

(5) SUMMARY OF THE INVENTION

Claims 11-13 and 19-22 define a nucleotide molecule encoding SR-BI, a protein normally expressed on the surface of certain cells, principally in the liver and tissues involved in steroidogenesis, which binds native as well as acetylated low density lipoprotein ("LDL") (page 6, lines 30-35). Based on its binding affinity for acetylated LDL, the protein was classified originally as a scavenger receptor protein (page 6, lines 27-30). Claims 44-47 are drawn to a method for screening of compounds altering binding of LDL or modified LDL to the SR-BI protein encoded by the nucleotide molecule of claim 11. Claim 48 is drawn to a method for removing LDL from a patient's blood by binding to immobilized SR-BI. Claim 49 is drawn to a method for inhibiting uptake of lipids and lipoproteins by adipocytes by inhibiting binding of the lipids or lipoproteins to the SR-BI protein encoded by the nucleotide molecule of claim 11. Claim 50 is a method for screening of patients with SR-BI having abnormal binding function.

Scavenger receptor proteins are described in the application at pages 1-3, and their structure shown in Figures 1A and B. SR-BI has a very different structure than the other scavenger receptor proteins (Figure 1B). However, it is classed as a scavenger receptor protein since it binds modified LDL (Figure 3A) as well as a number of other ligands (Figure 3B) (page 16, line 5, to page 17, line 8, and page 22, line 22, to page 24, line 21 and page 24, line 35-page 27, line 21). Its binding activity is similar to, but distinct from, other scavenger receptor proteins since it binds native LDL (Figure 3B) and high density lipoprotein ("HDL") (see page 19, lines 9-28, and Figure 8A). SR-BI's binding activity is also distinct from the similar but different

molecule, CD36 (page 27, line 34, to page 29, line 12; also, compare Figure 3B and Figure 4B and see Figure 5).

SR-BI was cloned initially from a hamster cell line by screening for scavenger receptor proteins binding to acetylated LDL (page 22, line 23, to page 24, line 21) (page 24, line 22, to page 25, line 34). A plasmid containing this cDNA was transfected into other cells and shown to express a protein binding acetylated LDL (page 26). The hamster SR-BI cDNA was then sequenced, analyzed and used as a hybridization probe to obtain a cDNA encoding the murine SR-BI (page 27, lines 22-32). Cells transfected with the isolated cDNA were further characterized for their binding activity (page 28, line 12, to page 31, line 10). Various tissues were then screened for expression of SR-BI and it was demonstrated to be preferentially expressed in steroidogenic tissues (page 31, line 11, to page 33, line 5). As noted at page 33, lines 34-36, SR-BI was believed to be responsible for cholesterol delivery to steroidenic tissues and liver. SR-BI is now known to be the only protein known to be involved in cholesterol transport. The specification exemplifies direct and competitive binding studies for use in the claimed methods as described above. More specific information on screening of patient samples and hybridization probes is provided at pages 40-41 and 43-50.

(6) ISSUES ON APPEAL

The issues presented on appeal are:

(1) whether claims 11-13, 19-22 and 44-50 are enabled under 35 U.S.C. § 112, first paragraph,

(2) whether claims 11-13, 19-22 and 44-50 are adequately described in the specification pursuant to 35 U.S.C. §112, first paragraph;

(2) whether claims 11-13, 19-22 and 44-50 are clear and definite as required by 35 U.S.C. § 112, second paragraph;

(3) whether claims 11, 13, 19, 20 and 22 lack novelty under 35 U.S.C. § 102(a) over Calvo et al., J Biol Chem (1993), 268(25): 18929-18935 ("Calvo"); and

(4) whether claim 21 is obvious under 35 U.S.C. § 103(a) over Calvo et al., J Biol Chem (1993), 268(25): 18929-18935 ("Calvo").

(7) GROUPING OF CLAIMS

Appellants submit that the claims do not stand or fall together.

Claims 11-15 and 19-22 are drawn to an isolated nucleic acid molecule that encodes a type BI scavenger receptor protein, alone or in combination with an expression vector or cell for expression thereof. Claims 14 and 15, which are specific for molecules having SEQ ID NO:3 and 4, respectively, have been allowed. Claim 19 defines a molecule defining a human scavenger receptor protein. Claim 21 defines the molecule in an expression vector. Claim 22 defines the molecule in a host cell.

Claims 44-47 are method claims. Since each method requires different reagents, different method steps, different starting materials, and different motivation to combine as appellants' have done, the method claims must be analyzed separately.

Claims 44-47, drawn to a method for screening for compounds altering binding of LDL or modified LDL to a scavenger receptor protein, which does not require the nucleic acid molecule of claims 11-13 and 19-22.

Claims 44 and 47 are drawn to a method for screening for a compound which alters the binding of scavenger receptor protein type BI as defined by the application. The method involves providing reagents for use in an assay for binding of low density lipoprotein or modified low density lipoprotein to the scavenger receptor protein, adding the compound to be tested to the assay, and then determining if the amount of modified low density lipoprotein or low density lipoprotein which is bound to the scavenger receptor protein is altered as compared to binding in the absence of the compound to be tested.

Claim 45 is drawn to the method of claim 44 but limits the assay for binding to a cell expressing the scavenger receptor protein, *which occur naturally and for which sources are identified in the application.*

Claim 46 is drawn to the method of claim 44 but further limits the compound to one that is selected from a library of compounds by randomly testing for alteration of binding.

Claim 48, drawn to a method for removing LDL from blood by reacting the blood to SR-BI protein, which does not require the nucleic acid molecule of claims 11-15 and 19-22. The blood is reacted with immobilized scavenger receptor protein type BI under conditions wherein the low density lipoprotein is bound to the scavenger receptor.

Claim 49, drawn to a method for inhibiting uptake of lipoprotein or lipids by adipocytes by inhibiting binding of the lipoprotein to the SR-BI, which does not require the nucleic acid

molecule of claims 11-13 and 19-22. The method involves selectively inhibiting binding of lipoprotein to the scavenger receptor protein type BI under conditions wherein the low density lipoprotein is bound to the scavenger receptor.

Claim 50, drawn to a method for screening patients for abnormal scavenger receptor protein or function by determining the presence, quantity or function of the SR-BI and comparing it to that present in normal cells, which does not require the nucleic acid molecule of claims 11-13 and 19-22.

(8) ARGUMENTS

(a) The Claimed Invention

As discussed above under grouping of the claims, the claims are broadly divided into two groups: claims drawn to isolated nucleic acid molecules that code for scavenger receptor proteins that are characterized by a defined binding affinity and methods for screening based on binding of the scavenger receptor proteins. The methods can be further divided based on the reagents and steps by which a particular object is achieved: (1) screening of compounds altering binding of SR-BI to LDL or modified LDL; (2) removing LDL from blood by reacting the blood with immobilized SR-BI; (3) inhibiting uptake of lipoproteins or lipids in adipocytes by inhibiting binding of the LDL to SR-BI; and (4) screening patients for abnormal SR-BI by measuring the amount or function of the SR-BI and comparing it to SR-BI in normal cells.

SR-BI is defined in the specification based on its three dimensional structure (see Figure 1B), amino acid sequence (SEQ ID Nos. 4 and 8), and binding activity (binds native LDL, modified LDL when in the presence of 10% serum, and HDL). It has been demonstrated to be

unique in all three areas, and to exhibit complete identity in three dimensional structure and functional activity across all species and have very high sequence identity between species (see, for example, the printouts of the amino acid sequences for the SR-BI cloned from hamster, rat, mouse, human and cattle, showing the similarity between the proteins, as well as the hamster (SEQ ID NO 4) and murine (SEQ ID NO 8) amino acid sequences provided in the application). Further, from the latter, one can readily determine which amino acids are conserved between species and critical function. Moreover, it is possible to detect SR-BI from one species with the DNA from another. As described in the application, Northern blot analysis of murine tissues was conducted using the hamster DNA), to show that SR-BI is most abundantly expressed in fat and is present at moderate levels in lung and liver. One skilled in the art, reading the phrase "SR-BI" or "scavenger receptor protein type BI" would know that this referred to a very particular type of protein. Based on the tissue expression data in the application, as well as the binding data, one skilled in the art would also know that it is involved in lipid transport, that it is highly unusual because it binds both native and modified LDL, that it binds cholesterol and HDL, and that it plays a role in steroidogenesis and transport of cholesterol to the liver, unlike any other scavenger receptor protein.

SR-BI, and the nucleic acid molecules encoding SR-BI, were not known to exist prior to cloning and expression of the SR-B1 receptor from hamster and then murine cells by appellants. Appellants obtained the DNA encoding the receptor while conducting studies to extend the analysis of the structure and function of mammalian modified lipoprotein scavenger receptors, using standard screening assays for lipoprotein binding by proteins expressed from DNA

obtained from a variant Chinese hamster ovary cell line (Var-261, which also expresses an apparently novel polyanion binding scavenger receptor distinct from SR-BI). Since many proteins are known to bind to lipoproteins, especially modified lipoproteins, the protein obtained from the Chinese hamster ovary cell line was characterized based on its binding specificity and compared to other known receptors, such as SR-A and CD36, a plasma membrane glycoprotein present in a restricted number of cell types, including platelets, monocytes, and some types of endothelial, epithelial, and melanoma cells. Not only is the binding specificity of these two proteins different, the cDNA encoding SR-BI yields a predicted protein sequence of 509 amino acids which is only approximately 30% identical to those of the three previously identified CD36 family members.

SR-BI is an important, highly conserved protein, playing a critical role in cholesterol transport. Once one has the protein and the isolated DNA encoding protein, from any species, it is possible to make antibodies to the protein or hyridization probes which can be used to screen patients or tissues for expression of SR-BI in levels or with function that is not normal (claim 50); it can be used as a target in a screening procedure for drugs which bind to SR-BI to alter lipid or lipoprotein uptake or transport (claims 44-47 and 49); and it can be immobilized and used to remove LDL from a patient's blood (claim 48). None of these methods require any reagents not explicitly described and demonstrated in actual examples in the application.

(b) Rejections Under 35 U.S.C. § 112

i. Rejection of Claims 11-13, 19-22 and 44-50 under 35 U.S.C. § 112, first paragraph (enablement)

The Legal Standard

The Court of Appeals for the Federal Circuit (CAFC) has described the legal standard for enablement under § 112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art, without undue experimentation (*See, e.g., Genentech, Inc. v. Novo Nordisk A/S*, 108 F3d at 165, 42 USPQ2d at 1004 (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also *In re Fisher*, 427 F.2d at 839, 166 USPQ at 24; *United States v. Telectronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988); *In re Stephens,* 529 F.2d 1343 (CCPA 1976)). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (*M.I.T. v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985)). In addition, as affirmed by the Court in *Spectra-Physics, Inc. v. Coherent, Inc.,* 827 F.2d 1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art.

Whether the disclosure is enabling is a legal conclusion based upon several underlying factual inquiries. See *In re Wands*, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir. 1988). A determination of undue experimentation is a conclusion based on weighing many factors, not just a single factor. Many of these factors have been summarized in *In re Forman,* 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986) and set forth in *In re Wands*. They are:

(1) The quantity of experimentation necessary (time and expense); (2) The amount of direction or guidance presented; (3) The presence or absence of working examples of the invention; (4) The nature of the invention; (5) The state of the prior art; (6) The relative skill of those in the art; (7) The predictability or unpredictability of the art; and (8) The breadth of the claims.

In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.' *Atlas Powder Co., v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984). There is no requirement for examples.

The Examiner's attention is drawn to the Board of Appeals decision in the parent of this application, U.S.S.N. 08/265,428, which contains no more disclosure than the present application.

The Board begins on page 7 with a discussion of the legal requirements for enablement, noting that the standard is whether one of skill in the art is able to practice the claimed invention at the time the application was filed without undue experimentation, stating in relevant part:

"nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples", quoting from In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971) . The Board then notes that the burden is on the *examiner* to provide a reasonable explanation of why the specification does not enable the claimed invention.

This standard was further clarified by the Court of Appeals for the Federal Circuit in *Amgen, Inc. v. Hoechst Marion Roussel, Inc. and Transkaryotic Therapies, Inc.*, 314 F.3d 1313 (Fed. Cir. 2003). As the Court stated:

> Both the written description and enablement requirements are defined by 35 U.S.C. § 112, first paragraph, which states that the patent specification must contain "a written description of the invention, and of the manner and process of making and using it...[such] as to enable any person of ordinary skill in the art to which it pertains ... to make and use the same ... " The purpose of the written description requirement is to prevent a patentee from later asserting that he invented something which he did not. Thus the patentee must "recount his invention in such detail that his future claims can be determined to be encompassed within his original creation." *Vas- Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1561, 19 U.S.P.Q.2d 1111, 1115 (Fed. Cit 1991). The purpose of the enablement requirement is to teach those or ordinary skill in the art how to make and use the invention without "undue experimentation." The specification does not need to teach what is already known in the art. The specification is enabled if one of ordinary skill in the art only engages in routine experimentation to make the invention.

Claims 11-13 and 19-22 are Enabled by the Specification

Appellants have demonstrated actual reduction to practice in the application as filed (1) isolation of a nucleotide molecule encoding SR-BI from a first species (hamster) and (2)

isolation of a nucleotide molecule encoding SR-BI from a second species (mouse). Appellant's Declarations under 37 C.F.R. 1.131 and 1.132 demonstrates that this information was sufficient to screen data bases to obtain sequence encoding the human analog. In minutes, appellants were able to identify the human sequence using the high degree of homology and conserved sequence between the two species previously isolated and characterized, and that of the human sequence.

Appellants have proven that they enable claims to the nucleotide molecule encoding SR-BI from multiple species and that others could use the same information and techniques to isolate the genomic DNA and polymorphs of the DNA encoding human SR-BI proteins. The examiner has provided no evidence that one skilled in the art would not expect to be able to isolate the homologous nucleotides molecules from any number of other representative widely divergent species.

It is unclear what the basis of the rejection is, other than that the claims are clearly intended to encompass the genus of nucleotide molecules encoding SR-BI, defined in terms of its primary (amino acid sequence) and secondary structure (Figure 1B) as well as functional activity (binding). Attention is drawn to appellants' declaration under 37 C.F.R. 1.132 in support of enablement. These statements must be considered absent actual evidence, not mere conjecture or argument, to the contrary. The examiner has apparently ignored the explanation and evidence provided for how one can isolate a genomic DNA using a cDNA. It was routine to screen genomic libraries using cDNA hybridization probes at the time of filing the present application (see Exhibits 6-8, submitted with the declaration under 37 C.F.R. 1.132). The hybridization conditions such as temperature and salt concentration can be adjusted to decrease the stringency

of the probe hybridization. A lower stringency condition would allow for a probe to bind sequences that were very similar but not identical to the cDNA probe. This would be ideal for screening genomic libraries from different species for homologous sequences. Additional proof of this is shown by reference to U.S. Patent No. 5,998,141 to Acton, which the Board cited in its decision in this case. cDNA encoding SR-BI, just as appellants describe in their application, was not only used to isolate the genomic DNA encoding SR-BI, but also polymorphic variations. See example 1, beginning at col. 32, line 54. See also col. 17, lines 8-38, stating that the same hybridization conditions were used, and can be used, to isolate genomic DNA encoding SR-BI from different species and including polymorphs or allelic variations. Accordingly, the examiner's statements to the contrary are simply wrong.

One of skill in the art would have known in 1994 how to make, or obtain, a human genomic library and synthesize a radiolabeled cDNA probe with routine experimentation. Probing nitrocellulose filters with the radiolabeled cDNA probe was already established and widely used in the art. These techniques were established and used routinely for at least 10 years prior to the filing of this application. Therefore one could isolate either genomic DNA or DNA encoding polymorphs, as defined by the claims, with only routine experimentation.

The specification provides a clear and enabling disclosure of these methods. The previously submitted declaration under 37 C.F.R. 1.132 referred to specific passages in the specification wherein general methods using nucleic acid probes to isolate genomic DNA sequences *via* libraries (page 10, lines 2-20); using nucleic acid probes (page 25, lines 10-20); and making genomic libraries (paragraph bridging pages 34 and 35) are all described.

Furthermore, the specification provides sufficient guidance for one skilled in the art to make and use a functional scavenger receptor encoded by the nucleic acid molecule of claim 11. As defined by claim 11, the receptor's functionality is centered on binding to 1) LDL, or 2) modified liproprotein having the characteristics of acetylated low density lipoprotein, in cell medium containing 10% serum. Appellants have clearly demonstrated that this screening method is routine by expressing both cDNAs and showing the binding of the SR-BI encoded thereby, using standard binding assays. That is all that is legally required. Page 40, lines 14-16, states that one would *typically* screen for expression of *functional* receptor. Pages 16 and 17 describe well known methods used for measuring receptor binding (and uptake and degradation). Such methods were well described in references dating back to 1983 and 1991 (Krieger and Freeman; see lines 8 and 9 of page 16). The *in vitro* binding activity of SR-BI is shown in Figures 2A,B and C, 3A and 3B, 5, 6, and 7. The *in vitro* binding specificity is compared to CD36 in Figures 4A, B and 5. This in combination with the materials and methods described in the application are clearly enabling to show the function of SR-BI. The *in vivo* function in the binding of cholesteryl esters in HDL is shown in Figure 8A, B and also described, and shown diagramatically in Figure 9.

The examiner's statements that the structure of SR-BI is not defined are absurd - the nucleotide sequence defines specific amino acid sequence. The tertiary structure of the protein encoded by this amino acid sequence is shown in Figure 1B. Moreover, the claims drawn to the protein, and variants thereof, have been allowed and issued as a U.S. Patent in the parent application, following appeal to the Board of Appeals.

The claims do not mention SEQ ID NO:4 or SEQ ID NO:8. The claims are directed to nucleic acid molecules encoding a functional scavenger receptor protein type BI. The terms "SEQ ID NO:4" and "SEQ ID NO:8" are nowhere to be found in the pending claims. As stated above, the claims are directed to *nucleic acid molecules* encoding a functional scavenger receptor protein type BI. Moderately stringent hybridization conditions (at a temperature of approximately 25°C below the melting temperature of a perfectly base-paired double-stranded DNA molecule, which one of ordinary skill in the art would know would consist of SEQ ID NO:3 or SEQ ID NO:7, just as the examiner has noted) allows for some variation in the nucleic acid sequence. However, the extent of this variation is precluded by the fact that what is encoded must be a receptor that binds to LDL or modified lipoprotein under the conditions defined by the claim.

In quoting the M.P.E.P §2164.08(a), the Examiner appears to be confusing structure (means) and the stated property (function) in the present claims. SEQ ID NO:3 and SEQ ID NO:7 are the two structural means used in defining the claimed nucleic acid molecules. These structural means, coupled with the explicitly stated stringency conditions in combination with the encoded amino acid sequence have the defined function and structure shown in Figure 1B, are all that is required to clearly define the claimed nucleic acid molecules. It is worthwhile to note that the claimed nucleic acids bind to SEQ ID NO:3 or SEQ ID NO:7 by virtue of their chemical structure *which is complementary* to the chemical structure of the target sequence. Antigen is also bound by antibodies by virtue of their chemical structure which is complementary to the chemical structure of the antibodies. *The structure is not complementary in the sense that one*

strand of DNA binds to a complementary strand of DNA, but complementary in that the three dimensional structure as well as the chemical composition is complementary to the three dimensional structure and chemical composition of the target sequence.

Claim 19 is dependent from claim 11. As such, it is necessary for the claimed molecule to hybridize to SEQ ID NO:3 and SEQ ID NO:7 under moderately stringent hybridization conditions. In view of the present specification and what was known in the art at the time of filing the present specification (as discussed in the foregoing paragraphs), one of ordinary skill would realize that trial and error experimentation is not a requisite for isolating the molecule of claim 11 or claim 19. Indeed, **Appellants were able to use SEQ ID NO:3 to isolate SEQ ID NO:7 and their sequences to identify the human sequence from an available data base (See Krieger and Action declaration).** The claims do not make reference to "non-rodent" species. Either of SEQ ID NO:3 and SEQ ID NO:7 and an available library is all that is required, under moderately stringent conditions, to give structure to the claimed molecule. The Examiner even admits on page 21 of the Office Action mailed August 6, 2003 that one of skill in the art would reasonably predict that these sequences exist in different species.

In response to the Examiner's comments regarding P1-established libraries and cloning genes using cDNA, appellants have submitted a copy of Yang *et al.* (*Proc. Natl. Acad. Sci.* USA, Vol. 87, pp 7907-7911, 1990) clearly demonstrating that the technique of using recombinant phage for the purpose of library screening was well-established by 1990. Furthermore, Southern hybridization and restriction fragment length polymorphism (RFLP) analyses were commonly used techniques at the time of filing the present application (for example, see body of Yang *et*

al.). Two abstracts were also previously submitted (Rouleau *et al.*, *Genomics*, **1989**, 4(1):1-6; and Ioannou *et al.*, *Nat. Genet.* **1994**,6(1):84-9), illustrating the use of recombinant phage libraries enriched for human chromosome 22 sequences for use in RFLP analysis and P1 vectors for introducing recombinant DNA into *E. coli*, respectively. Using cDNA to aid in cloning entire genes would not have been undue at the time of filing the present application. Furthermore, chromosomal walking was a routine method used to clone many genes at the time of filing the application. The *application* of each *well known* technique to the particular situation that the researcher has carved out for him-/herself was routine. The examiner has admitted that library screening using probes from cDNA was routine (see page 16 of the office action mailed on August 6, 2003).

With respect to administration of compounds to block binding, attention is drawn to the examples and graphs showing inhibition of binding to the SR-BI. It is believed these *actual examples* fully demonstrate the use of compounds to inhibit SR-BI binding as claimed.

Lastly, once one has the SR-BI protein and/or the DNA encoding SR-BI, from any species, it is possible to make antibodies to the protein or hybridization probes which can be used to screen patients or tissues for expression of SR-BI in levels or with function that is not normal (claim 50); it can be used as a target in a screening procedure for drugs which bind to SR-BI to alter lipid or lipoprotein uptake or transport (claims 44-47 and 49); and it can be immobilized and used to remove LDL from a patient's blood (claim 48). None of these methods require any reagents not explicitly described and demonstrated in actual examples in the application.

In summary, one skilled in the art to which claims 11-13 and 19-22 pertain, cloning of a scavenger receptor protein, would have been able to obtain a nucleotide molecule encoding human SR-BI with no more than routine experimentation, as of the priority date of this application (June 23, 1994), based on the disclosure by appellants using commercially available reagents and standard techniques.

While it is true that the specificity of nucleic acid interaction, or hybridization, can be affected by the conditions that the hybridization occurs under, those of skill in the art know how to perform hybridization experiments that lead to specific gene recognition of homologues, and the present application **specifically describes** how to do this for a SR-B1 cDNA. For example, on page 18, line 27 to page 19, line 6, there is an explicit description of a hybridization procedure in which the isolated hamster SR-B1 cDNA is used to produce a 600 base probe (derived from a BamHI restriction digest of the DNA shown in SEQ ID No. 3) which is used to probe different cell types from murine tissues and from 3T3 cells. The hybridization and washing conditions were done at 42° C and 50° C respectively using the well known conditions described by Charron et al. *Proc. Natl. Acad. Sci.* 86 2535-2539 (1989). Performing the hybridization analysis as described in the application clearly shows that a single predominant band of 2.4 kb was abundant in fat and present in moderate levels in lung and liver (page 31:line 11 to page 32:line 24). While the 600 base probe derived from the hamster scavenger receptor type B1 cDNA hybridizes as a single gene sequence in mouse, a probe from CD36 has a different hybridization pattern, indicating that the hybridization assay described is sufficient to differentiate between CD36 and Appellants' nucleic acids encoding SR-B1 type proteins. This fact is significant since, as pointed

out by the Examiner, other non-SR-BI genes are closely related in sequence to hamster and human SR-BI sequence (see Calvo et al.). This indicates that while CD36 and SR-B1 are related proteins (both members of the CD36 superfamily), they are not so related as to be considered homologues with each other and one skilled in the art would not interpret a reference to SR-BI as being the same as a reference to CD36. CD36 is also excluded from the scope of the claims due to the binding specificity requirement: as shown in Figure 5, graphing competitive binding of acetylated LDL to either SR-BI or CD36 in the presence of native LDL, SR-BI binds native LDL and CD36 does not.

In summary, one skilled in the art, reading the claim which includes not only the phrase "hybridization" in conjunction with a defined sequence as well as the functional activity ("binding specificity") of the SR-BI would know exactly what was defined by the claims. The claims are therefore definite, and enabled, by the specification.

Claims 11-13, 15, 19-22 were also rejected under §112, first paragraph, on the basis that the "claims encompass nucleic acids encoding proteins whose amino acid sequences have been substantially altered from their natural forms whereas the instant specification does not provide the guidance that is required to produce such nucleic acids in a predictable manner."

First, its should be noted that the mere fact that claims encompass embodiments that are not explicitly described, nor exemplified, does not render the claims non-enabled. In fact, inclusion of some embodiments that are even inoperative would still not render the claims non-enabled.

As articulated by this Board in *Ex parte Mark*, 12 U.S.P.Q.2d 1904 (Bd. Pat. App. & Int'f 1989), "When it is considered that the claims remaining on appeal all require that the mutein produced retain the biological activity of the native protein, we consider the disclosure of this application to be enabling . . . The fact that a given protein may not be amenable for use in the present invention in that the cystein residues are needed for the biological activity of the protein does not militate against a conclusion of enablement. One skilled in the art is clearly enabled to perform such work as needed to determine whether the cysteine residues of a give protein are needed for retention of biological activity." 12 U.S.P.Q.2d at 1906-1907.

As applied to the claims here on appeal, one skilled in the art can obtain starting material merely by reference to the application before him. He can readily compare the amino acid sequences for the hamster and mouse SR-BI proteins and determine which amino acids are conserved and which are not. He can enter the amino acid sequence into computer programs that were commercially available in 1994 and look at the resulting structure, to determine which amino acids are located at critical regions. Even if an amino acid is changed, intentionally or accidentally or by nature, it would require no more than routine effort to screen for activity. The assays to screen for binding activity are detailed in the application and the expected ranges actually demonstrated. The minimal nature of the experimentation required to obtain these proteins is demonstrated by how appellants, with no knowledge of the existence of this protein nor its activity, were able to screen *an entire expression library* for activity, as they did to originally isolate the SR-BI from hamster cells. See in particular the studies reported at page 36, in which *3500 clones were screened initially for activity, then subdivided into 18 subpools of 350*

clones which were transfected into cells and screened again. Appellants also demonstrated that they were able to obtain the mouse SR-BI DNA using the hamster DNA, with no more than routine effort. With the sequences of SR-BI proteins from two different species, and their activity profiles in hand, as well as the requirement that the nucleic acid hybridize to these known sequences, and encode a protein having the structure as shown in Figure 1B (i.e, encode a scavenger receptor BI protein), it would only require routine testing to determine which molecules are encompassed by the claims.

The CCPA first addressed the issue of protein variants in *In re Fisher*, 427 F.2d 833 (CCPA, 1970). Integral to this holding was the court's reliance on the knowledge of one of ordinary skill in the art, and the lack of a showing that one of ordinary skill in the art could obtain sequences other than 39 amino acids long. The court stated,

> The parent specification does not enable one skilled in the art to make or obtain ACTHs with other than 39 amino acids in the chain, and *there has been no showing that one of ordinary skill would have known how to make or obtain such other ACTHs without undue experimentation.* As for Appellant's conclusion that the 25th to 39th acids in the chain are unnecessary, *it is one thing to make such a statement when persons skilled in the art are able to make or obtain ACTH having other than 39 amino acids*; it is quite another thing when they are not able to do so.
>
> Id. at 836. (emphasis added).

It is clear that the court was placing great emphasis on what one of ordinary skill in the art could have hoped to make or obtain. This decision was handed down in 1970, on an application filed November 29, 1960, claiming priority from an application filed June 9, 1954. The priority application was filed one year after Watson and Crick determined that the structure of DNA was a double helix (Watson and Crick *Nature* 171, 964-967 (1953)). It would still take seven years of research before scientists even knew that there was a triplet code between a DNA sequence and a protein sequence (Crick et al. *Nature* 192 1227-1232 (1961)). It is not reasonable to assume that a holding, based on an application filed in 1954, prior to the advent of biotechnology, is controlling on biotechnology itself. The court in *In re Fisher* very likely correctly held that "one could not make or obtain", without undue experimentation, a protein with less than 39 amino acids . . . *in 1954*. The court just as correctly noted though that if one of ordinary skill in the art could have made or obtained such a protein then the holding would have been very different. *Unlike this case*, appellants have demonstrated that one of ordinary skill in the art of cloning *in 1994* can obtain other nucleotide molecules encoding SR-BI with the requisite activity, without undue experimentation.

The court in *Amgen, inc. v. Chugai Pharmaceutical Co., LTD.*, 927 F.2d 1200 (Fed. Cir. 1991) relied heavily on the holding in *In re Fisher* to find a claim drawn to a large number of non-natural Erythropoietin (EPO) analogs invalid for failing to meet the requirements of 35 U.S.C. 112. The court focused on the number of possible analogs that were encompassed by the claim **and** on the uncertainty held by the Appellant as to which analogs, already produced, possessed the activity. The trial court relied on expert testimony which provided that "Amgen is

still unable to specify which analogs have the biological properties set forth in the claim." *Id.* at 1213. The Federal Circuit chose to focus on the making and using of the DNA sequences, which produce the protein which has the biological activity, rather than the biological activity itself. While the *Amgen* court spoke positively of *In re Angstadt*, 537 F.2d 498, 502, which held that it is not necessary that a patent Appellant test all embodiments of his invention, just that he provide a sufficient disclosure to enable one skilled in the art to practice the full scope of the claims, they stated that for claims based on DNA sequences a sufficient disclosure meant, "disclosing how to make and use enough sequences to justify grant of the claims sought." *Id.* at 1213. The court went on to state, "what is relevant *depends on the facts*, and the facts here are that Amgen has not enabled *preparation of DNA sequences* sufficient to support its all-encompassing claims." *Id.* at 1213. (emphasis added). Again, as in *In re Fisher*, the focus is on what Appellants, or one of ordinary skill in the art, could do. The court focused on whether the preparation of the DNA sequences, within the scope of the claims, could *be prepared.* The application at issue was filed on November 30, 1984 and claimed priority to an application filed on December 13, 1983. Therefore, the "facts" relevant to the "preparation of DNA sequences" in the courts mind were those that existed in 1983. This is almost four years prior to the advent of PCR. Chemical synthesis of DNA was still only able to routinely produce short oligonucleotides. In short, the two most important technological advances for the "preparation of DNA sequences" in a manner without "undue experimentation", PCR and highly efficient automated DNA synthesis, were still years away. A case decided based on the level of skill in the art *ten years earlier*, in a field

changing almost hourly, cannot be used as a basis for a determination of what one skilled in the art would do as of 1994.

In *Hormone Research Foundation v. Genentech, Inc.* 904 F.2d 1558, 1568-69 (Fed. Cir. 1990), the court reversed a summary judgement for lack of enablement regarding claims directed to human growth hormone. The lower court had ruled that the alleged infringer had presented sufficient evidence indicating that the application was not enabled to merit summary judgement. (*Hormone Research Foundation v. Genentech, Inc.*, 708 F.Supp 1096 (N.D.Cal. 1988). The Federal Circuit remanded this issue for further adjudication because the lower court had failed to adequately address the analysis of *In re Hogan*, 559 F.2d 959 (CCPA 1977) and *United States Steel Corp. v. Phillips Petroleum Co.* 865 F.2d 1247 (Fed. Cir. 1989). In commenting on the relevance of these cases the *Hormone Research Foundation* court stated,

> It is unclear whether the high degree of potency and purity contemplated by the district court's analysis of enablement was influenced by the *potency and purity obtainable through recombinant DNA methodology*. Moreover, it is unclear from the record before us *whether that technology existed at the time the application was filed.* Further factual development as to the *state of the art at the date of the application* . . . is required for this court to review the enablement issues.
>
> *Id.* at 1568-1569. (emphasis added).

The meaning and intent of the court is clear: one must assess the question of enablement in the light of the knowledge of one of ordinary skill in the art *at the time the application is filed.* In this case, Appellants have demonstrated one can obtain and screen huge numbers of molecules rapidly and without experimentation, and that it is possible to routinely obtain additional molecules encoding SR-BI merely by hybridization to one of the disclosed nucleotide molecules.

A central issue in the above cases is the level of predictability in the art. The question remains, however, as to what "unpredictability" means. For example, the court in *In re Vaeck* 947 F.2d 497 (Fed. Cir 1991) addressed the issue of unpredictability by stating, "we do *not* imply that patent applications in art areas currently denominated as unpredictable must never be allowed generic claims encompassing more than the particular species disclosed in their specification." *Id.* at 496. (emphasis contained in original). The court went on to state that "there must be sufficient disclosure . . . to teach those of ordinary skill how to make and how to use the invention . . ." *Id.* at 496. The question remains, what is a sufficient disclosure for an application that is in an "unpredictable" art? The clear answer given by the court was "the disclosure must adequately guide the art worker to determine, *without undue experimentation*, which species among all those encompassed by the claimed genus possess the disclosed utility. *Id.* at 496. (emphasis added). The court did **not** state, "without any experimentation," they stated "without undue experimentation". This means that a standard of "predictability" that excludes "all" experimentation is simply incorrect.

"Unpredictability" is often used as a sword by the PTO to slash the scope of a legitimate biotechnology claim. The sharpness and size of this sword, however, are unduly exaggerated

because of the misapplication of what is and should be "predictable". In the area of functional variants, such as discussed in *In re Fisher* or *Amgen Inc., v. Chugai Pharmaceutical Co.,* the standard when assessing whether the specification enables one of ordinary skill in the art to make and use the claimed variants is whether it would require "undue experimentation" to determine which variants are functional. In the language of *In re Vaeck*, "the disclosure must adequately guide the art worker to determine, *without undue experimentation*, which species among all those encompassed by the claimed genus possess the disclosed utility. *Id.* at 496.

The priority date for the application on appeal is June 23, 1994. By this time technologies such as PCR were highly developed and were routinely utilized to "prepare" DNA molecules which encoded for variants of known protein sequences. The importance of utilizing PCR cannot be overestimated with respect to the manipulation of DNA molecules, and specifically the insertion, deletion or substitution of DNA sequences which lead to changes in the amino acid sequence of a protein. The specification contains ample description of recombinant DNA methods that enable one of ordinary skill in the art to make SR-B1 receptors with varied amino acids. For example, on page 51 the subsection entitled "Preparation of Receptor Protein Fragments" describes numerous methods including cleaving the protein with various proteases, expression of the altered protein from a recombinant DNA molecule, and even chemical synthesis of the desired protein fragment. On page 52:lines 14-18 the specification states, "These methods can be used to synthesize peptides having identical sequence to the receptor proteins described herein, or substitutions or additions of amino acids, which can be screened for activity."

The "preparation of the DNA molecules" encoding the variants of the sequences disclosed in SEQ ID NOs. 4 and 8 are fully enabled by the specification. Likewise, the assays to determine those variants that have the desired activity are readily described. The claims require that the nucleic acids encoding the SR-B1 receptor are capable of hybridizing with either SEQ ID. Nos. 3 or 7, and that they encoding proteins selectively binding to low density lipoprotein and modified lipoprotein. Assays for determining whether the modified DNA molecules hybridize to SEQ ID Nos. 3 or 7 are described at least from page 18:line 27 to page 19:line 6. As is indicated in these pages these methods were published in 1992, approximately three years before the priority date of the application. Clearly one of ordinary skill in the art would be able to practice techniques that were nearly three years old. In addition the application describes a number of assays that indicate whether a candidate SR-B1 protein binds low density lipoprotein and modified lipoprotein as required by the claims. For example, on page 19 there is a subsection entitled "HDL Binding Studies" and following this section is the description of "Phospholipid Binding and Competition Assays." On page 21 there is yet another section entitled "Ligand Binding Assays" that discloses methods for determining if various low density lipoproteins and modified lipoproteins bind cells containing candidate SR-B1 receptors.

The Examiner is clearly falling into the trap of interpreting "predictability" as prediction without **any** experimentation. This standard is absolutely inconsistent with the standard of "undue experimentation" set up in *In re Forman* and reiterated in *In re Wands*. The very word "predictability" is one of the factors to *determine* whether undue experimentation exists, not whether *any* experimentation should be commenced at all. It is a misapplication of the *Wands*

standard to first ask the question "is it predictable which variant *a priori* has activity?", and then if the answer from the Examiner's position is "no" to forgo the undue experimentation analysis. This is clearly putting the proverbial cart before the horse. As Judge Rich illustrated in *In re Vaeck*, "the disclosure must adequately guide the art worker to determine, *without undue experimentation*, which species among all those encompassed by the claimed genus possess the disclosed utility. *Id.* at 496. Clearly, "predictability" does not supercede the standard of "undue experimentation" and the making of a DNA molecule encoding a variant of a SR-B1 receptor and testing this receptor for activity and characteristics required by the claims, in the technological world of 1994 is **not** undue experimentation.

The requirement by the Examiner that the specification contain working examples misconstrues the law and misconstrues the facts of the application. The legal standard does not require "working examples" in the specification, it is merely one of the factors which may be considered in a determination of undue experimentation. On page 5 of the Advisory Action mailed August 3, 1998, the Examiner states, "*Wands* now requires that one consider the number of working examples presented in the instant specification." This is false. The Federal Circuit explicitly stated in *Amgen, inc. v. Chugai Pharmaceutical Co., LTD.*, "it is not necessary that a court review all the *Wands* factors to find a disclosure enabling" *Id.* at 1213. Thus, the specification does not require working examples to meet the correct standard which is undue experimentation.

Notwithstanding the above, the specification does provide working examples showing the isolation and characterization of nucleotide molecules encoding SR-B1 proteins having different

amino acid sequences that meet all of the requirements of the claims, the hamster homologue of SR-B1 and the murine homologue of SR-B1. While the Appellants have not described in the application making "synthetic" variants of the SR-B1 protein, nature has provided the necessary evidence that there are protein variants of the hamster SR-B1 that exist which meet the limitations of the claims. There are numerous positions in the amino acid sequence of the murine homologue to the hamster SR-B1 that are "variant" from the hamster SR-B1 sequence. The application teaches one how to make the protein variants, the application teaches one how to test the protein variants for activity, and the application teaches one that not every amino acid is required for function as required by the claims. The latter demonstration is what a working example can provide for an application, and this demonstration is provided by the fact that multiple homologues are disclosed.

The *Wands* factors do not require the "making of record prior art" as indicated by the Examiner at page 3 of the Advisory Action mailed on August 3, 1998. First, it is not required that all of the *Wands* factors be addressed to find that a claim does not require undue experimentation. Second, "making art of record" is not even one of the specific factors suggested. The nearest suggested analysis is "the state of the prior art." There is no requirement that all which is known to one of ordinary skill in the art be submitted to the Patent Office either in the form of the specification or in the art made of record.

Notwithstanding the above, the prior art made of record, while not explicitly required by the *Wands* factors, clearly supports the enablement of protein variants. For example, Cullen et al, "Use of Eukaryotic Expression Technology in the Functional Analysis of Cloned Genes,"

Methods in Enz. 152:684-704 (1987) describes numerous methods for producing eukaryotic expression vectors, such as those used in the present specification, to test specific DNA sequences for activity. Methods for domain swapping and protein mutagenesis were readily known to those of ordinary skill in the art and this is exemplified by Daugherty, et al., "Polymerase chain reaction facilitates the cloning, CDR-grafting and rapid expression of a murine monoclonal antibody directed against the CD18 component of leukocyte integrins," *Nucl. Acids Res.* 19:2471-2476 (1991).and Itakura et al., "Synthesis and use of synthetic oligonucleotides," *Ann. Rev. Biochem.* 53:323-356 (1984). Daugherty et al. describes methods for using the Polymerase Chain Reaction (PCR) to swap functional domains of a specific antibody between the murine and human homologues. Itakura et al. actually discusses site mutagenesis prior to PCR and describes this technology, in 1984, by saying "The once seemingly obvious limitations of this technique [referring to site directed mutagenesis] –availability of synthetic DNA and a knowledge of the nucleotide sequence of the target region—are no longer major factors." *Id.* at 343-344. Thus, in 1984, 10 years before the priority date of this application, the opinion of those of ordinary skill in the art was that the factors which arguably caused undue experimentation to make protein variants prior to 1984, "are no longer major factors" after 1984.

iii. Claims 44-50 are enabled

As discussed above, claims 44-50 are distinct from the claims drawn to nucleotide molecules. Each of these methods can be performed as described in the application as originally filed, without preparation of any nucleotide molecules encoding an SR-BI other than those explicitly exemplified.

The claimed methods in conjunction with the specification are absolutely clear and complete. One of skill in the art would be able to practice, without undue experimentation, the claimed methods. For example, the Examiner has singled out the recitation of "providing reagents for use in an assay for binding" in claim 44, as incomplete. The specification provides numerous examples of reagents for binding, such as AcLDL and M-BSA to name two. Page 28:line 15 to page 31:line 10 provides an extensive description of binding assays and binding reagents. Claims 44-50 are complete in their recitation of the necessary steps which set out the claimed methods. As outlined in *In re Miller*, 441 F.2d 689, 169 USPQ 597 (CCPA 1971), the breadth of a claim is not to be equated with indefiniteness.

a. Claims 44 and 47 are fully enabled

Claims 44 and 47 are fully enabled by the specification and separately patentable. Claims 44 and 47 are drawn to methods for screening for compounds which alter the binding of the low density lipoproteins to the SR-B1 receptor. *These are not drawn to the compounds themselves.* The method comprises the steps of providing reagents for binding assays of low density or modified low density lipoproteins, adding the compound to be tested, and determining if the amount of low density or modified low density lipoprotein binding to SR-B1 is altered. The specification provides ample support for this method on pages 43 to 51.

b. Claim 45 is fully enabled

Claim 45 is fully enabled by the specification and is separately patentable. Claim 45 is drawn to the methods of claim 44 with the further limitation of requiring the assay include expression of the scavenger receptor protein in a cell, where the inhibiting molecule is a nucleic

acid which alters expression of the scavenger receptor protein. On page 47, a section entitled, "Generation of nucleic acid regulators" describes methods to design and isolate nucleic acid molecules which inhibit the expression of a variety of proteins, including scavenger receptors.

c. Claim 46 is fully enabled

Claim 46 is separately patentable and fully enabled by the specification. Claim 46 is drawn to the method of claim 44 wherein the compounds tested are selected from a randomly screened library. This further limitation of the claim is fully supported in the application at page 45:lines 23-40. *In vitro* selection technologies and combinatorial chemistry approaches to the isolation of small molecule inhibitors are well known, and fully applicable to the isolation of molecules that inhibit SR-B1 binding to low density or modified low density lipoprotein.

d. Claim 48 is fully enabled

Claim 48 is fully enabled by the specification and is separately patentable. Claim 48 is drawn to the screening of patient blood samples and the removal of low density and modified low density lipoprotein from patient blood samples. Support for the limitations of this claim can be found on page 54:lines 9-15. Methods of attaching proteins to solid supports are described and well understood by those of ordinary skill in the art.

e. Claim 49 is fully enabled

Claim 49 was rejected under 35 U.S.C. §112, first paragraph, as allegedly not enabled by the specification. This rejection is solely based on the "intended use" of the claimed compositions. The Examiner has asserted that the specification fails to teach how to "use" the claimed compositions. This rejection was made under 35 U.S.C. § 112, first paragraph, but

really is nothing more than a rejection for lack of utility under 35 U.S.C. § 101. The claimed compositions and methods are fully enabled to make and use as required under 35 U.S.C. § 112, and have more than enough utility to meet the minimal standard required by the judicial interpretation of the utility requirement.

f. Claim 50 is fully enabled

Claim 50 is fully enabled and separately patentable. Claim 50 is drawn to a method of screening patients to determine if the patients have abnormal levels of SR-B1 receptor or abnormally functioning receptor. The method comprises determining if there is a scavenger receptor present that hybridizes to either SEQ ID NOs. 3 or 7 and binds low density or modified low density lipoprotein, and then determining if the quantity present is similar to normal cells and if the function of the SR-B1 receptor is similar to the SR-B1 receptors of normal cells. There are numerous assays for determining the amount of SR-B1 receptor present in a given cell. For example, from page 32:line 25 to page 33:line 5, methods using antibodies to recognize SR-B1 receptors are described. Those of ordinary skill in the art would readily know how to compare the amounts of SR-B1 protein in control cells to the cells of choice using these type of blotting techniques. The application also describes numerous binding assays to various low density and modified low density lipoproteins that characterizes SR-B1 function. One of ordinary skill in the art would know how to compare the binding capabilities of the control SR-B1 and the SR-B1 derived from the specific cell or patient being screened. Claim 50 is fully enabled, and therefore, should be found valid by the Appeal Board.

ii. Rejection of Claim 19 under 35 U.S.C. § 112, first paragraph (written description)

The Legal Standard

Both the written description and enablement requirements are defined by 35 U.S.C. § 112, first paragraph, which states that the patent specification must contain "a written description of the invention, and of the manner and process of making and using it...[such] as to enable any person of ordinary skill in the art to which it pertains ... to make and use the same ... " The purpose of the written description requirement is to prevent a patentee from later asserting that he invented something which he did not. Thus the patentee must "recount his invention in such detail that his future claims can be determined to be encompassed within his original creation." *Vas- Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1561, 19 U.S.P.Q.2d 1111, 1115 (Fed. Cit 1991).

For many years the leading case for the written description requirement in the biotechnology and pharmaceutical arts was *Eli Lilly v. Univ. of Calif. Board of Regents*, in *Regents of University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997), *cert denied*, 523 U.S. 1089 (1998). The Federal Circuit evaluated whether claims to recombinant production of human insulin in U.S. Patent No. 4,652,525 met the written description requirement. The court determined that the specification failed to comply with the written description requirement for only disclosing a single species of DNA encoding non-human insulin.

The Federal Circuit has since held that that the written description requirement can be met by a functional description of claimed materials, if coupled with a known or disclosed

correlation between function and structure. *Enzo Biochem, Inc., v. Gen-Probe, Inc.*, 296 F.3d 1316, 63 U.S.P.Q.2d 1609 (Fed. Cir.2002) ("*Enzo II*"). *Enzo II* states "the written description requirement to be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ... i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." This standard was subsequently affirmed and clarifed in the decision of *Amgen Inc. v. Hoechst Marion Roussel, Inc. and Transkaryotic Therapies, Inc.* 314 F.3d 1313, 65 USPQ 2d (Fed. Cir. 2003).

Claims 11-13, 19-22 meet the written description requirement

The rejected claims define nucleotide sequences by virtue of hybridization to listed nucleotide sequences, as well as by the amino acids which they encode that must form a structure as shown in Figure 1B, having the claimed activity. Appellants have provided the sequences to which the claimed nucleotides must hybridize, as well as the conditions, the three dimensional structure and the function. These features fully define the claimed nucleotide molecules. It is well established at this point that once one provides the structure and function, and has reduced to practice representative species of a genus (two in this case), one has complied with the written description requirements for the genus.

Furthermore, the issue of description is adequately met simply by constructively reducing the material to practice (*Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 19 USPQ2d 1111 (Fed. Cir. 1991)). The Court in *Vas-Cath Inc. v. Mahurkar* stated, "Whether the disclosure of the

application relied upon reasonably conveys to the skilled artisan that the inventor had possession at the that time [i.e., when the application was filed] of the later claimed subject matter." As long as the subject matter was described in the specification as it was claimed, the description requirement is met. Applying this standard, the human homologue as claimed in claim 19 clearly meets the description requirement.

Claim 19 defines a nucleotide molecule encoding a human SR-BI. Appellants acknowledge that the exact nucleotide sequence for this molecule is not recited in the application. However, while the examiner goes into a great deal of discussion regarding issues of species versus genus, acknowledging that Appellants have disclosed a species (actually two, the species from hamster and the species from mouse), he states at page 3 of the Office Action mailed March 19, 1998, that "Because the instant application does not provide a written description of those material properties which distinguish "a human scavenger receptor" from any other mammalian scavenger receptor, a practitioner of the art cannot produce the claimed nucleic acid to the exclusion of a nucleic acid encoding any other mammalian scavenger receptor." This statement is patently incorrect and nonsensical.

First, appellants are not claiming any human scavenger receptor; they are only claiming SR-BI, which is characterized as having a defined structure, amino acid sequence as found in two different species, increased expression in certain types of cells, and a unique binding activity. No other scavenger receptor binds both native and acetylated LDL. No other scavenger receptor binding both native and acetylated LDL can be obtained by routine screening of tissues using a probe from either of the two nucleotide sequences from hamster and mouse that are

provided. Appellants also provide two nucleotide molecules encoding SR-BI and which are complementary to the nucleotide molecule encoding human SR-BI under defined conditions. Appellants demonstrate that it is possible to use a probe from one species to identify DNA encoding the same protein from a second species, as discussed above. Appellants were able to identify the actual human sequence from a data base using the murine and hamster sequences. There are no unique features of human SR-BI that makes it necessary to define human SR-BI any differently than for any other species, other than there are a few nucleotides differences. Indeed, as demonstrated from abstracts from a few subsequently published papers, the human SR-BI is extremely similar in amino acid sequence and identical in binding activity, binding both native and acetylated LDL, which appellants have demonstrated can be routinely used to obtain DNA encoding an SR-BI protein from species other than the species for which nucleotide sequence is known.

In so far as the Examiner is relying on *Regents of the University of California v. Eli Lilly and Company*, 43 USPQ2d. 1398 (CAFC 1997) as the basis for this rejection, Appellants note that *Regents of U.C.* is not applicable since the claims and underlying specification here are not analogous to the facts there. The Court in *Regents of U.C.* relied on the fact that the description of example 6 in the patent at issue prophetically described obtaining a cDNA sequence from the **protein** sequence of the human protein. This is completely different than the situation here, where the specification relies on the use of the homologous cDNA as a probe, not a degenerate sequence obtained by reverse translation of a protein sequence. This difference is absolutely critical because the court in *Regents of U.C.* relied on their own precedence of *In re Deuel* 51

F.3d 1552, 1558, 34 USPQ2d 1210, 1215 (1995). The court stated, "A prior art disclosure of the **amino acid sequence** of a protein does not necessarily render particular DNA molecules encoding the protein obvious because the redundancy of the genetic code permits one to hypothesize an enormous number of DNA sequences encoding for the protein." In relying on the relationship of amino acid sequence to nucleic acid sequence, *Regents of U.C.* is limited to protein-to-DNA situations. It should be noted that the court in *Regents of U.C.* did not specifically address (and thus, did not overrule) the standard that has been accepted for the description requirement for the last 125 years, most recently explicated in *Vas-Cath Inc. v Mahurkar*. Notwithstanding the above, it is noted that only decisions handed down by an *en banc* panel of the Federal Circuit are sufficient to overrule previous case law. In this respect, the decisions of the Federal Circuit in *Eli Lilly* and its progenitor cases do not overrule the longstanding positions taken by the courts on the description requirements. (*Vas-Cath Inc. v Mahurkar).*

Claims 44-50 meet the written description requirement

a. Claims 44 and 47 meet the written description requirement

Claims 44 and 47 are fully supported by the specification and separately patentable. Claims 44 and 47 are drawn to methods for screening for compounds which alter the binding of the low density lipoproteins to the SR-B1 receptor. *These are not drawn to the compounds themselves.* The method comprises the steps of providing reagents for binding assays of low density or modified low density lipoproteins, adding the compound to be tested, and determining

if the amount of low density or modified low density lipoprotein binding to SR-B1 is altered. The specification provides ample support for this method on pages 43 to 51.

b. Claim 45 meet the written description requirement

Claim 45 is fully supported by the specification and is separately patentable. Claim 45 is drawn to the methods of claim 44 with the further limitation of requiring the assay include expression of the scavenger receptor protein in a cell, where the inhibiting molecule is a nucleic acid which alters expression of the scavenger receptor protein. On page 47, a section entitled, "Generation of nucleic acid regulators" describes methods to design and isolate nucleic acid molecules which inhibit the expression of a variety of proteins, including scavenger receptors.

c. Claim 46 meet the written description requirement

Claim 46 is separately patentable and fully supported by the specification. Claim 46 is drawn to the method of claim 44 wherein the compounds tested are selected from a randomly screened library. This further limitation of the claim is fully supported in the application at page 45:lines 23-40. *In vitro* selection technologies and combinatorial chemistry approaches to the isolation of small molecule inhibitors are well known, and fully applicable to the isolation of molecules that inhibit SR-B1 binding to low density or modified low density lipoprotein.

d. Claim 48 meet the written description requirement

Claim 48 is fully supported by the specification and is separately patentable. Claim 48 is drawn to the screening of patient blood samples and the removal of low density and modified low density lipoprotein from patient blood samples. Support for the elements of this claim can

be found on page 54:lines 9-15. Methods of attaching proteins to solid supports are described and well understood by those of ordinary skill in the art.

e. Claim 49 meet the written description requirement

Claim 49 is fully supported by the specification and is separately patentable . Claim 49 is drawn to a method for inhibiting uptake of lipoprotein or lipids by adipocytes. Support for this claim is found on page 38, lines 1-11 and page 44, lines 3-22. Methods of administration are well understood by those of ordinary skill in the art.

f. Claim 50 meet the written description requirement

Claim 50 is fully supported and separately patentable. Claim 50 is drawn to a method of screening patients to determine if the patients have abnormal levels of SR-B1 receptor or abnormally functioning receptor. The method comprises determining if there is a scavenger receptor present that hybridizes to either SEQ ID NOs. 3 or 7 and binds low density or modified low density lipoprotein, and then determining if the quantity present is similar to normal cells and if the function of the SR-B1 receptor is similar to the SR-B1 receptors of normal cells. There are numerous assays for determining the amount of SR-B1 receptor present in a given cell. For example, from page 32:line 25 to page 33:line 5, methods using antibodies to recognize SR-B1 receptors are described. Those of ordinary skill in the art would readily know how to compare the amounts of SR-B1 protein in control cells to the cells of choice using these type of blotting techniques. The application also describes numerous binding assays to various low density and modified low density lipoproteins that characterizes SR-B1 function. One of

ordinary skill in the art would know how to compare the binding capabilities of the control SR-B1 and the SR-B1 derived from the specific cell or patient being screened.

iii. Rejection of Claims 11-13 , 19-22 and 44-50 under 35 U.S.C. § 112, second paragraph

The Legal Standard

The legal standard for definiteness states that "definiteness of claim language must be analyzed, not in a vacuum, but in light of:

A) The content of the particular application disclosure

B) The teachings of the prior art

C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

In reviewing a claim for compliance with 35 U.S.C. 112, second paragraph, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and therefore, serves the notice function required by 35 U.S.C. 112, second paragraph. See, e.g. Solomon v Kimberly-Clark Corp., 216 F.3d 1372, 1379, 55 USPQ2d 1279, 1283 (Fed.Cir. 2000) (MPEP 2173.02)

The patentable subject matter should be defined with a "reasonable degree of particularity and distinctness". "Some latitude in the manner of expression and the aptness of terms should be permitted even though the claim language is not as precise as the Examiner might desire." (MPEP 2173.02)

Claims 11-13 and 19-22 Meet the Definiteness Requirement

The Examiner's suggestions at page 7 of the Office Action mailed on August 6, 2003, have been noted but are not believed to be necessary. The standard is whether one skilled in the art would know what is defined by the claim. Clearly the examiner fully understands what is meant by the claims, as would others skilled in the art. Attention is drawn to the issued parent, also defining the nucleotide molecules in the same terms, as well as the Acton patent described above (U.S. Patent No. 5,998,141) . Hundreds of other patents have also issued using the language now pending in this application. Accordingly, the claim language meets the requirements of 35 U.S.C. 112, second paragraph, as well as distinguishes the claimed polynucleotides from those encoding CD36.

Scavenger receptor protein type BI and the functions of this protein are described thoughout the specification. Features of scavenger receptor proteins are defined on pages 1-6 in the background of the invention. Binding properties are defined on pages 7 and 11-13 for example. Figures 3, 5, 7, and 8 all describe functions and binding of SR-BI.

The claim element defining hybridization conditions to which a sequence binds is also definite. The claims define a molecule that binds to SEQ ID NO: 3 or SEQ ID NO:7 under moderately stringent conditions. The skilled artisan in molecular biology would readily comprehend what is necessary to obtain moderately stringent hybridization conditions. Salt concentration and temperatures and wash times would all be adjusted appropriately. The conditions are in reference to the probes which in this instance are SEQ ID NO:3 and SEQ ID NO:7 which are two defined nucleotide molecules. One would understand what hybridization

conditions were required to bind to either of these molecules based on knowledge of skill in the art and the defined conditions in the specification that are also included in the claims.

With respect to the issue regarding whether the cDNA encoding SR-BI from two species is adequate to define the cDNA encoding SR-BI from other species, the examiner is referred to the foregoing discussion on enablement, and the previously submitted Declarations under 37 C.F.R. 1.131 and 1.132 (and as referred to, and discussed, above).

Claims 44-50 meet the definiteness requirement

a. Claims 44 and 47 are definite

Claims 44 and 47 are definite and separately patentable. Claims 44 and 47 are drawn to methods for screening for compounds which alter the binding of the low density lipoproteins to the SR-B1 receptor. *These are not drawn to the compounds themselves.* The method comprises the steps of providing reagents for binding assays of low density or modified low density lipoproteins, adding the compound to be tested, and determining if the amount of low density or modified low density lipoprotein binding to SR-B1 is altered. The specification provides ample support for this method on pages 43 to 51 and defines the conditions needed to alter SR-BI binding.

b. Claim 45 is definite

Claim 45 is definite and is separately patentable. Claim 45 is drawn to the methods of claim 44 with the further limitation of requiring the assay include expression of the scavenger receptor protein in a cell, where the inhibiting molecule is a nucleic acid which alters expression of the scavenger receptor protein. On page 47, a section entitled, "Generation of nucleic acid

regulators" describes methods to design and isolate nucleic acid molecules which inhibit the expression of a variety of proteins, including scavenger receptors. These claim elements are definite to one of skill in the art and in few of the teachings of the specification.

c. Claim 46 is definite

Claim 46 is definite and fully supported by the specification. Claim 46 is drawn to the method of claim 44 wherein the compounds tested are selected from a randomly screened library. This further limitation of the claim is fully supported in the application at page 45:lines 23-40. As stated previously, i*n vitro* selection technologies and combinatorial chemistry approaches to the isolation of small molecule inhibitors are well known, and fully applicable to the isolation of molecules that inhibit SR-B1 binding to low density or modified low density lipoprotein. The skilled artisan would readily comprehend what is defined by this claim.

d. Claim 48 is definite

Claim 48 is definite and is separately patentable. Claim 48 is drawn to the screening of patient blood samples and the removal of low density and modified low density lipoprotein from patient blood samples. Support for the elements of this claim can be found on page 54:lines 9-15. Methods of attaching proteins to solid supports are described and well understood by those of ordinary skill in the art. The claim elements are defined by the specification and in combination with knowledge in the art.

e. Claim 49 is definite

Claim 49 is definite and is separately patentable . Claim 49 is drawn to a method for inhibiting uptake of lipoprotein or lipids by adipocytes. Support for this claim is found on page

38, lines 1-11 and page 44, lines 3-22. Methods of administration are defined and are well understood by those of ordinary skill in the art.

f. Claim 50 is definite

Claim 50 is definite and separately patentable. Claim 50 is drawn to a method of screening patients to determine if the patients have abnormal levels of SR-B1 receptor or abnormally functioning receptor. The method comprises determining if there is a scavenger receptor present that hybridizes to either SEQ ID NOs. 3 or 7 and binds low density or modified low density lipoprotein, and then determining if the quantity present is similar to normal cells and if the function of the SR-B1 receptor is similar to the SR-B1 receptors of normal cells. There are numerous assays for determining the amount of SR-B1 receptor present in a given cell. For example, from page 32, line 25 to page 33, line 5, methods using antibodies to recognize SR-B1 receptors are described. As stated previously, hybridization techniques are well established in the art. Those of ordinary skill in the art would readily know how to compare the amounts of SR-B1 protein in control cells to the cells of choice using these type of blotting techniques. The application also describes numerous binding assays to various low density and modified low density lipoproteins that characterizes SR-B1 function. One of ordinary skill in the art would know how to compare the binding capabilities of the control SR-B1 and the SR-B1 derived from the specific cell or patient being screened.

(c) Rejections Under 35 U.S.C. § 102

i. Rejection of Claims 11, 13, 19, 20 and 22 under 35 U.S.C. § 102(a) over Calvo et al., J Biol Chem (1993), 268(25): 18929-18935 ("Calvo").

The Legal Standard

For a rejection of claims to be properly founded under 35 U.S.C. § 102, it must be established that a prior art reference discloses each and every element of the claims. *Hybritech Inc v Monoclonal Antibodies Inc*, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 US 947 (1987); *Scripps Clinic & Research Found v Genentech Inc*, 18 USPQ2d 1001 (Fed. Cir. 1991). The Federal Circuit held in *Scripps*, 18 USPQ2d at 1010:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. . . *There must be no difference* between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. (Emphasis added)

A reference that fails to disclose even one limitation will not be found to anticipate, even if the missing limitation could be discoverable through further experimentation. As the Federal Circuit held in *Scripps, Id.*:

> [A] finding of anticipation requires that all aspects of the claimed invention were already described in a single reference: a finding that is not supportable if it is necessary to prove facts beyond those disclosed in the reference in order to meet the claim limitations. The role of extrinsic evidence is to educate the decision-

maker to what the reference meant to persons of ordinary skill in the field of the invention, not to fill in the gaps in the reference.

For a prior art reference to anticipate a claim, it must enable a person skilled in the art to practice the invention. The Federal Circuit held that "a §102(b) reference must sufficiently describe the claimed invention to have placed the public in possession of it. . . [E]ven if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling." *Paperless Accounting Inc v Bay Area Rapid Transit Sys.*, 231 USPQ 649, 653 (Fed. Cir. 1986) (citations omitted).

Legal analysis of 1.131 Declarations

37 C.F.R. § 1.131 states, in pertinent part,

> (a)(1) When any claim of an application . . . is rejected under 35 U.S.C. 102 (a) or (e), or 35 U.S.C. 103 based on . . . reference to . . . a printed publication, the inventor of the subject matter of the rejected claim . . . may submit an appropriate oath or declaration to overcome the . . . publication. The oath or declaration must include facts showing a completion of the invention in this country or in a NAFTA or WTO member country before . . . the date of the printed publication.
>
> * * *

> (b) The showing of facts shall be such, in character and weight, as to establish reduction to practice prior to the effective date of the reference, or conception of the invention prior to the effective date of the reference coupled with due diligence from prior to said date to a subsequent reduction to practice . . . .

The Appellant need only provide evidence that reasonably gives rise to an inference that the invention was completed before the reference date, in order to constitute a *prima facie* showing. No corroboration is required since the application process is *ex parte*. A Rule 131 affidavit is sufficient when it demonstrates that the Appellant has prior "possession" of that part of the invention disclosed by the reference, as is the case when a reference discloses a species falling within a claim to its genus. *See* Donald S. Chisum, **Patents** § 3.08[1][b] (Matthew Bender & Co. 1996). Possession in this context is shown by demonstrating conception, reduction to practice, and diligence--each as normally required in determining the date of invention. *See In re Mulder*, 716 F.2d 1542 (Fed. Cir. 1983).

In *In re Stempel*, 241 F.2d 755 (C.C.P.A. 1957), the court held that Appellant's affidavit under Rule 131 was not required to show priority with respect to the claimed genus, but only to the species disclosed by the cited reference, in order to remove that reference as prior art. The claims, both genus and species were drawn to chemical compounds. *Stempel* overcame the anticipation rejection by showing reduction to practice, prior to the effective date of the reference, of a species of the invention within the generic claims.

In *In re Tanczyn,* 347 F.2d 830 (C.C.P.A. 1965), the court qualified *In re Stempel*, stating that the *Stempel* doctrine did not apply to *partial* possession of the invention, as distinguished from *total* possession of a species within a genus claim. The *Tanczyn* application "did not involve a genus-species relationship." Id. at 833.

In *In re Clarke,* 356 F.2d 987 (C.C.P.A. 1966), the court extended the *Stempel* doctrine to the situation more at issue in this application, that is, where the Appellant's Rule 131 affidavit shows possession of representative species of the claimed genus, not of the specific species disclosed by the reference. The *Clarke* court held that the affidavit is sufficient to remove a reference where the Appellant demonstrates possession of such "invention" as to make the entire claimed invention or the reference part obvious to one of ordinary skill in the art. The court stated,

> "[i]n an appropriate case an Appellant should not be prevented from obtaining a patent to an invention where a compound described in a reference would have been obvious to one of ordinary skill in the art in view of what the affiant proves was completed with respect to the invention prior to the effective date of the reference. . . . Thus, we think that in an appropriate case a single species could be sufficient to antedate indirectly a different species of a reference.".

The CCPA also has phrased the rule, "[w]hen that species of the generic invention which has been completed prior to the effective date of the reference would make obvious to one of

ordinary skill in the art the species disclosed in the reference, the reference may be said to have been 'indirectly antedated.'" *In re Schaub*, 537 F.2d 509, 512 (C.C.P.A. 1976) (quoting *In re Ranier*, 390 F.2d 771, 773-74 (C.C.P.A. 1968)). The *Schaub* court stated that "[a]ppellants have made a *prima facie* case that the compound of the reference is obvious from the compounds which they have made prior to the date of the reference. Appellants' compound III is the next higher homolog of the reference compound II, . . ." Id. at 512-13.

There is little, if any, Federal Circuit case law on point. However, the rule established in *In re Clarke* apparently remains valid, as one somewhat recent, "unpublished" (i.e. not citable as precedent) case seems to indicate. In *In re Rozmus*, 928 F.2d 412, 1991 WL 17232 (Fed. Cir.), the court stated that "[a]lthough Rozmus' [Rule 131] declaration showed reduction to practice of only a species of the generic invention, that alone is not fatal to his claim. A declaration proving a species is also sufficient to show possession of 'variations and adaptations which would, at the same time, be obvious to one skilled in the art.'" (quoting *In re Spiller*, 500 F.2d 1170, 1178 n.5 (CCPA 1974)).

Other cases discussing priority but which do not involve Rule 131 have stated, "[p]riority as to a genus may . . . be shown by prior invention of a single species, but the genus will not be patentable to an Appellant unless he has generic support therefor." *In re Zletz*, 893 F.2d 319, 323 (Fed. Cir. 1989); *see also Hoffman v. Schoenwald* 15 U.S.P.Q.2d 1512, 1514 (Bd. Pat. App. & Int'f 1990) ("Conception of a species within the genus constitutes conception of the genus for priority of invention purposes.").

Claims 11, 13, 19, 20 and 22 are Novel

Appellants have clearly demonstrated conception and reduction to practice of the claimed genus prior to Calvo. Therefore Calvo should not be available as prior art to claims 11, 13, 20 and 22. The only claim in issue is claim 19, drawn to the DNA encoding the human SR-BI protein.

Calvo, et al. reported isolation of a cDNA encoding a member of the CD36 superfamily. The protein was not physically isolated nor was the cloned DNA expressed, much less expressed on the surface of cells and shown to be functional, although a small piece non-functional portion (the carboxyl terminal region including residues 365-409) was expressed as a chimeric protein (page 18930). The function of the protein was not known, although its resemblance to CD36/LimpII was recognized based on the predicted similarities in structure and the authors speculated that "on the basis of its structural homology to CD36 that CLA-1 could act as a receptor for extracellular products" (page 18934).

As demonstrated repeatedly by Appellants and discussed above, CD36 and SR-BI are *not* the same proteins nor do they have the same binding activity.

A Declaration under 37 C.F.R. §1.131, submitted in the parent application, U.S. Serial No. 08/265,428, filed June 23, 1994, which demonstrates that a cDNA and encoded protein defined by the claims in issue was conceived and reduced to practice prior to the publication of Calvo, et al. was submitted with the Response to An Office Action, mailed on December 29, 1997. Appellants cloned the gene, they expressed the protein, and they characterized the protein and showed its function, **prior to** Calvo's publication date.

The Examiner has stated that the Declaration under Rule 1.131 does not "demonstrate that the Appellants was in possession of the any information regarding a CLA-1 protein or CLA-1 gene from any animal other than hamster prior to the publication of Calvo et al." Appellants respectfully point out that this is not in fact true. Submitted with the Declaration is a printout obtained from the search of six databases (PDP, Swissprot, PIR, SPupdate, Genpept, GPupdate). This printout indicates that the Rat LimpII gene and the CD36 gene were among the genes with the highest homology to SR-B1. While these genes have been shown to be members of a different families within the superfamily of CD36 scavenger receptors than the SR-B1 proteins of the present application, for one of ordinary skill in the art they presented a nexus between the species described in the Declaration of Krieger and Acton and the genus which would include the CLA-1 gene described in Calvo et al. The validity of these assertions is evidenced by the fact that the CLA-1 gene was isolated using primers derived from CD-36 and LIMP II, related but non-homologous proteins. Surely, the possession of the homolog of the CLA-1 protein, with the information that it fell within the CD-36 superfamily, is more information than Calvo et al. had when they cloned the CLA-1 gene, but not the homolog, from rat. The Appellants clearly were in possession of the genus of SR-B1 proteins and nucleic acid molecules that encode these proteins prior to the publication of Calvo.

Furthermore, the Examiner has stated, "There is no evidence in this Declaration that a nucleic acid probe encoding all or part of hamster CLA-1 was capable of hybridizing to mouse DNA or that a DNA encoding a murine cDNA had been isolated." This statement is incorrect. The latter is obviously wrong - SEQ ID NO. 7 *is* the nucleic acid sequence encoding the murine

SR-BI. Moreover, the specification provides exactly the type of evidence the Examiner is looking for. For example, on page 18:line 27 to page 19:line 6 there is an explicit description of a hybridization procedure in which a 600 base probe of derived from the hamster SR-B1 cDNA is used to probe different cell types from murine tissues and from 3T3 cells. The results from these experiments clearly shows that a single predominant band of 2.4 kb was abundant in fat and present in moderate levels in lung and liver (page 31:line 11 to page 32:line 24). This data not only directly indicates an interspecies hybridization abundance, it indicates that this relationship is specific and successful because it recognizes the murine homologue in only those tissues that express it. The genus of the claims is described as cDNAs encoding Scavenger Receptor Protein type B1, having specific functional properties, and includes the SR-B1 cDNA of the present application and the CLA-1 cDNA of Calvo et al. This genus is a subgenus of the genus of CD36 superfamily of scavenger receptor proteins which includes CD36 and LimpII.

To one of ordinary skill in the art there would have been more than sufficient motivation given the sequence homology data presented in the Declaration to utilize the information obtained from the novel hamster SR-B1 to isolate the human homologue based on the information provided in the specification and the general knowledge known in the art. The claimed sequence would have been obvious due to the high degree of homology and sequence identity, the exact same protein structure and function, and the ready available of reagents and methods enabling the isolation of the nucleotide molecule.

The claimed sequences are novel because Calvo et al. has been antedated by the Krieger and Acton Rule 1.131 Declaration. Furthermore, the nature of the art is such that upon obtaining

the sequences of the haSR-B1 and the murine SR-B1 those of ordinary skill in the art would have found it obvious to obtain the homologs to these nucleic acid molecules for the reasons outlined above.

The declaration also establishes prior conception of the genus and representative species, followed by diligent reduction to practice of the human species.

Calvo et al. does not disclose, nor has Calvo et al. been alledged to disclose, the expression of the proteins encoded by the nucleic acid molecules described in claim 11 in adipocyte, lung, or liver cells. As discussed above, these limitations are fully enabled in the present application and render the claims novel over Calvo et al.

Claim 19 is novel and separately patentable over Calvo et al. because as discussed above the Rule 1.131 Declaration presented by Drs. Krieger and Acton prove that the Appellants were in possession of the claimed subject matter prior to the publication of Calvo et al. Furthermore, as discussed above, the inventive efforts of the Appellants made obvious the cloning of other SR-B1 homologs and therefore, the 1.131 Declaration is sufficient to antedate a "different species" within the genus.

(d) Rejections Under 35 U.S.C. § 103

i. Rejection of Claim 21 under 35 U.S.C. § 103(a) over Calvo et al., J Biol Chem (1993), 268(25): 18929-18935 ("Calvo").

The Legal Standard

The law is quite clear that, for the Patent Office to establish a *prima facie* case of obviousness of claimed subject matter, the prior art references relied upon must provide *both* a

suggestion to make the claimed invention and a reasonable expectation of success. It is also clear that the whole field of the invention must be considered, including those publications which teach away from the claimed invention. Particularly relevant to the matters under consideration here are the decisions of the Court of Appeals for the Federal Circuit in *In re Dow Chemical*, 5 USPQ2d 1529 (1988) and *In re Vaeck*, 20 USPQ2d 1438 (1991). The *Dow* Court noted that:

> The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in light of the prior art.... Both the suggestion and expectation of success must be founded in the prior art, not in the Appellant's disclosure.
>
> In determining whether such a suggestion can fairly be gleaned from the prior art, *the full field of the invention must be considered*: for the person of ordinary skill is charged with knowledge of the entire body of technological literature, including that which might lead away from the claimed invention.... Evidence that supports, rather than negates, patentability must be fairly considered.

5 USPQ 2d at 1531-1532 (Citations omitted, emphasis added).

In *In re Dow Chemical*, a combination of three components forming an impact resistant rubber-based resin was not found to be obvious based upon art disclosing the individual components. The court noted that the record had shown that the claimed combination had

previously been made, *but did not produce the product desired.* "That there were other attempts, and various combinations and procedures tried in the past, does not render obvious the later successful one.... Recognition of need, and difficulties encountered by those skilled in the field, are classical indicia of unobviousness," *Id.* at 1531 (citations omitted). The Court found that none of the prior art cited by the Appellant and the PTO suggested that any process could be used successfully in this three-component system to produce the product having the desired properties. Further, the Court stated that evidence from an expert expressing skepticism as to the success of the claimed combination before these inventors proved him wrong should be considered. *Id.* at 1532.

Claims 21 is not obvious in view of Calvo et al.

The Board stated in their decision at page 13 "we remind the examiner, if the prior art does not teach any specific or significant utility for the disclosed compounds, then the prior art is not sufficient to render structurally similar claims *prima facie* obvious because there is no motivation for one of ordinary skill in the art to make the reference compounds, much less any structurally related compounds. *In re Stemniski*, 444 F.2d 581, 586, 170 USPQ 343, 348 (CCPA 1971).

As discussed above, the Krieger and Acton Declaration clearly shows that the Appellants were in possession of the cDNA and expressed protein prior to the date of Calvo et al. Therefore, Calvo et al. is antedated and not effective as 35 U.S.C. § 103 art.

However, even it if were available as prior art, it cannot make obvious the genus where there was no expression of a protein, nor recognition of its properties.

Among the reasons that the Examiner has argued that it would be obvious to go from the Human CLA-1 gene described by Calvo et al. to the hamster homologue are: (1) CLA is described as being structurally analogous to LIMPII: (2) amino acid sequence were highly conserved between human and rat LIMPII; (3) the genes had sufficient similarity to permit the isolation of LIMPII; (4) an artisan would have concluded that any mammalian protein encoding CLA-1 would have been readily isolated by probing a DNA library, since the hamster, as well as rat, was routinely employed as a laboratory model for determining the physiological significance of proteins of human origin since the scope of human experimentation is obviously limited, (5) and there was knowledge that there was homology between humans and rodents at the time. [Appellants note, in passing, that each and every one of these reasons, relied upon by the Examiner to support the "*prima facie*" case of obviousness to clone the hamster SR-B1 protein from the sequence information of the human CLA-1 protein were presented in the specification and Declaration in the present application, and one must assume that the Examiner may have used hindsight based on this Declaration to identify reasons why one would go from Calvo to what is claimed, rather than from what Appellants have demonstrated they conceived and reduced to practice, prior to Calvo, to arrive at what Calvo disclosed.]

Appellants do not understand how, in the light of the Declaration submitted, the Examiner can maintain that it was *prima facie* obvious to clone the hamster homologue of the human CLA-1 when Appellants have demonstrated possession of the hamster gene before the date of the publication of the human homologue CLA-1. Furthermore, in light of the Examiner's rejection of claim 19 under 35 U.S.C § 112 for an inadequate description of the human

homologue of SR-B1, which implicitly relies on *Regents of the University of California v. Eli Lilly and Company*, 43 USPQ2d. 1398 (CAFC 1997), it is inconsistent to maintain a rejection which is contrary to the Examiner's only interpretation and reliance on case law. Appellants have distinguished themselves not only from *Regents of the University of California v. Eli Lilly and Company* (as discussed above), but also assert that in the light of the Declaration and the evidence provided in the specification, it would have been *prima facie* obvious to clone the human homologue of SR-B1 from what Appellants had well prior to the publication by Calvo!

Appellants have demonstrated that they cloned and expressed the hamster gene encoding the claimed SR-BI proteins, and that the gene hybridizes to the murine gene, prior to publication by Calvo et al. Accordingly, Appellants conceived of and reduced to practice the claimed invention prior to Calvo et al. Therefore, the Declaration under 37 C.F.R. §1.131 should conclusively remove Calvo et al. as a reference, and the claims found patentable to Appellants.

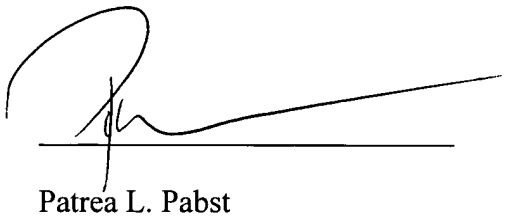
Claim 21 is not made obvious by Calvo et al. Calvo et al. does not disclose the expression of the molecules of claim 11 in either adipocytes, lung cells, or liver cells, nor for that matter, in any cell type. The Examiner has failed to meet his burden of establishing a *prima facie* case of obviousness because there has been no showing that Calvo et al. ever expressed active, functional protein, knew what function to look for, or how to look for related proteins. In addition, there is nothing in Calvo et al. that would lead one to express the molecules of claim 11 in adipocyte, lung, or liver cells. Therefore, claim 21 is patentable over Calvo et al.

(9) SUMMARY AND CONCLUSION

In conclusion, claims 11-13, 19-22 and 14-50 are enabled under 35 U.S.C. § 112, first paragraph, because the limitation of hybridization and specific lipoprotein binding limit the claims and appellants have provided evidence that other variants and homologues from other species could be obtained using only routine methodology. The declaration by Dr. Krieger and Dr. Acton support the enablement of the disclosure in view of the knowledge in the art at the time of filing. Claims 11-13, 19-22 and 44-50 are not vague and indefinite under 35 U.S.C. §112, second paragraph. Claims 11, 12, 15, 19 and 20 are novel under 35 U.S.C. § 102(a) over Calvo *et al. J Biol Chem (1993), 268(25): 18929-18935 ("Calvo")* and claim 21 is not obvious under U.S.C. § 103 over Calvo *et al. J Biol Chem (1993), 268(25): 18929-18935 ("Calvo")* because the Rule 1.131 Declaration presented by Drs. Krieger and Acton show that the Appellants were in possession of the claimed subject matter prior to the publication of Calvo *et al.*

For the foregoing reasons, Appellant submits that the claims 11-13, 19-22, and 44-50 are patentable.

Respectfully submitted,



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Date: February 6, 2004

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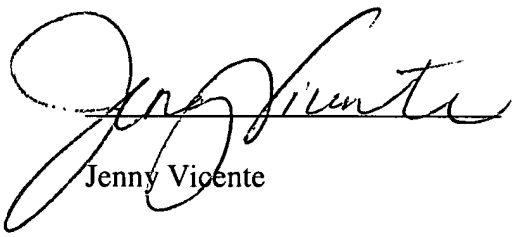
Certificate of Mailing Under 37 C.F.R. § 1.8(a)

I hereby certify that this Appeal Brief, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to Mail Stop Appeal Brief - Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.



Jenny Vicente

Date: February 6, 2004

Appendix: Claims On Appeal

1-10. (cancelled)

11. (previously presented) An isolated nucleic acid molecule encoding a functional scavenger receptor protein type BI which selectively binds to low density lipoprotein and to modified lipoprotein having the characteristics of acetylated low density lipoprotein in cell medium containing 10% serum, which hybridizes to SEQ ID Nos. 3 and 7 under moderately stringent hybridization conditions at a temperature of approximately 25°C below the melting temperature of a perfectly base-paired double-stranded DNA.

12. (previously presented) The molecule of claim 11 expressed in cells selected from the group consisting of adipocytes, lung cells and liver cells.

13. (previously presented) The molecule of claim 11 hybridizing under stringent hybridization conditions at a temperature greater than 25°C below the melting temperature of a perfectly base-paired double-stranded DNA to a molecule with Sequence ID No. 3.

14. (previously presented) An isolated nucleic acid molecule encoding a scavenger receptor protein having the sequence of Sequence ID No. 3.

15. (previously presented) An isolated nucleic acid molecule encoding a protein with the amino acid sequence shown in Sequence ID No. 4.

16-18. (canceled)

19. (previously presented) The molecule of claim 11 which encodes a human scavenger receptor.

20. (previously presented) The molecule of claim 11 labeled with a detectable label.

21. (previously presented) An expression vector comprising the molecule of claim 11 encoding the scavenger receptor protein.

22. (previously presented) A host cell comprising the nucleic acid molecule of claim 11.

23-43. (cancelled)

44. (previously presented) A method for screening for a compound which alters the binding of scavenger receptor protein type BI, which is encoded by a nucleotide molecule hybridizing to SEQ ID Nos. 3 and 7 under moderately stringent hybridization conditions at a temperature of approximately 25°C below the melting temperature of a perfectly base-paired double-stranded DNA and which selectively binds to low density lipoprotein and to modified lipoprotein having the characteristics of acetylated low density lipoprotein in cell medium containing 10% serum, comprising

providing reagents for use in an assay for binding of low density lipoprotein or modified low density lipoprotein to the scavenger receptor protein the reagents comprising SR-BI, low density lipoprotein or modified low density lipoprotein, and means for determining if the low density lipoprotein or modified low density lipoprotein is bound to the scavenger receptor protein,

adding the compound to be tested to the assay, and

determining if the amount of modified low density lipoprotein or low density lipoprotein which is bound to the scavenger receptor protein is altered as compared to binding in the absence of the compound to be tested.

45. (previously presented) The method of claim 44 wherein the assay includes a cell expressing the scavenger receptor protein and the compound is a nucleic acid molecule which alters expression of the scavenger receptor protein.

46. (previously presented) The method of claim 44 wherein the compound is selected from a library of compounds which are randomly tested for alteration of binding.

47. (previously presented) The method of claim 44 wherein the compound competitively inhibits binding of low density lipoprotein or modified lipoprotein having the characteristics of acetylated low density lipoprotein to the scavenger receptor protein.

48. (previously presented) A method for removing low density lipoprotein from patient blood comprising reacting the blood with immobilized scavenger receptor protein type B, wherein the scavenger receptor protein type BI is encoded by a nucleotide molecule hybridizing to SEQ ID Nos. 3 and 7 under moderately stringent hybridization conditions at a temperature of approximately 25°C below the melting temperature of a perfectly base-paired double-stranded DNA and selectively binds to low density lipoprotein and to modified lipoprotein having the characteristics of acetylated low density lipoprotein in cell medium containing 10% serum, under conditions wherein the low density lipoprotein is bound to the scavenger receptor.

49. (previously presented) A method for inhibiting uptake of lipoprotein or lipids by adipocytes comprising

administering a compound selectively inhibiting binding of lipoprotein to the scavenger receptor protein type BI, wherein the scavenger receptor protein type BI is encoded by a nucleotide molecule hybridizing to SEQ ID Nos. 3 and 7 and selectively binds to low density

lipoprotein and to modified lipoprotein having the characteristics of acetylated low density lipoprotein, under conditions wherein the low density lipoprotein is bound to the scavenger receptor.

50. (previously presented) A method for screening patients for abnormal scavenger receptor protein activity or function comprising

determining the presence of scavenger receptor protein type BI, wherein the scavenger receptor protein type BI is encoded by a nucleotide molecule hybridizing to SEQ ID Nos. 3 and 7 under moderately stringent hybridization conditions at a temperature of approximately 25°C below the melting temperature of a perfectly base-paired double-stranded DNA and selectively binds to low density lipoprotein and to modified lipoprotein having the characteristics of acetylated low density lipoprotein, and

determining if the quantity present or the function of the receptor is equivalent to that present in normal cells.

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(d) Rejections Under 35 U.S.C. § 103

i. Rejection of Claim 21 under 35 U.S.C. § 103(a) over Calvo et al., J Biol Chem (1993), 268(25): 18929-18935 ("Calvo").

(9) SUMMARY AND CONCLUSION

Certificate of Mailing

Appendix: Claims On Appeal

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants: Monty Krieger and Susan L. Acton

Serial No.: 08/765,108 Art Unit: 1646

Filed: March 27, 1997 Examiner: Michael T. Brannock

For: *CLASS BI AND CI SCAVENGER RECEPTORS*

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

Sir:

This is an appeal from the rejection of claims 11-13, 19-22 and 44-50 in the Office Action mailed August 6, 2003, in the above-identified patent application. A Notice of Appeal was mailed on December 8, 2003. A check in the amount of $330.00 for the filing of this Appeal Brief for a large entity is also enclosed.

It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-1868.

(1) REAL PARTY IN INTEREST

The real party in interest of this application is , the assignee Massachusetts Institute of Technology, Cambridge, Massachusetts.

(2) RELATED APPEALS AND INTERFERENCES

This is application was previously before the Board of Appeals as appeal number 2001-1495, remanded to the examiner in the decision dated September 25, 2001. There is one other related appeal known to appellant, the undersigned, or appellant's assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal, the appeal in the parent application, U.S. Serial No. 08/265,428 entitled "Class BI and CI Scavenger Receptors" filed June 23, 1994 by Monty Krieger and Susan Acton.

Please note that the inventorship of this application was amended in the Preliminary Amendment mailed December 23, 1996, cancelling claims 1-8 and 23-43, since Atillio Rigotti is not an inventor of the remaining claims. The inventorship was clarified by the Examiner in the Office Action mailed March 5, 2002 on page 3.

(3) STATUS OF CLAIMS ON APPEAL

Claims 11-15, 19-22, and 44-50 are pending. Claims 14 and 15 are allowable. Claims 1-8 and 23-43 were cancelled in the Amendment mailed December 23, 1996. Claims 9 and 10 were cancelled in an Amendment mailed February 11, 1999. Claims 16-18 were cancelled in an Amendment mailed December 29, 1997. Claims 11-13, 19-22 and 44-50 are on appeal. The text of each claim on appeal, as pending, is set forth in an Appendix to this Appeal Brief.

(4) STATUS OF AMENDMENTS

The claims were last amended in the amendment mailed February 10, 2003.

(5) SUMMARY OF THE INVENTION

Claims 11-13 and 19-22 define a nucleotide molecule encoding SR-BI, a protein normally expressed on the surface of certain cells, principally in the liver and tissues involved in steroidogenesis, which binds native as well as acetylated low density lipoprotein ("LDL") (page 6, lines 30-35). Based on its binding affinity for acetylated LDL, the protein was classified originally as a scavenger receptor protein (page 6, lines 27-30). Claims 44-47 are drawn to a method for screening of compounds altering binding of LDL or modified LDL to the SR-BI protein encoded by the nucleotide molecule of claim 11. Claim 48 is drawn to a method for removing LDL from a patient's blood by binding to immobilized SR-BI. Claim 49 is drawn to a method for inhibiting uptake of lipids and lipoproteins by adipocytes by inhibiting binding of the lipids or lipoproteins to the SR-BI protein encoded by the nucleotide molecule of claim 11. Claim 50 is a method for screening of patients with SR-BI having abnormal binding function.

Scavenger receptor proteins are described in the application at pages 1-3, and their structure shown in Figures 1A and B. SR-BI has a very different structure than the other scavenger receptor proteins (Figure 1B). However, it is classed as a scavenger receptor protein since it binds modified LDL (Figure 3A) as well as a number of other ligands (Figure 3B) (page 16, line 5, to page 17, line 8, and page 22, line 22, to page 24, line 21 and page 24, line 35-page 27, line 21). Its binding activity is similar to, but distinct from, other scavenger receptor proteins since it binds native LDL (Figure 3B) and high density lipoprotein ("HDL") (see page 19, lines 9-28, and Figure 8A). SR-BI's binding activity is also distinct from the similar but different

molecule, CD36 (page 27, line 34, to page 29, line 12; also, compare Figure 3B and Figure 4B and see Figure 5).

SR-BI was cloned initially from a hamster cell line by screening for scavenger receptor proteins binding to acetylated LDL (page 22, line 23, to page 24, line 21) (page 24, line 22, to page 25, line 34). A plasmid containing this cDNA was transfected into other cells and shown to express a protein binding acetylated LDL (page 26). The hamster SR-BI cDNA was then sequenced, analyzed and used as a hybridization probe to obtain a cDNA encoding the murine SR-BI (page 27, lines 22-32). Cells transfected with the isolated cDNA were further characterized for their binding activity (page 28, line 12, to page 31, line 10). Various tissues were then screened for expression of SR-BI and it was demonstrated to be preferentially expressed in steroidogenic tissues (page 31, line 11, to page 33, line 5). As noted at page 33, lines 34-36, SR-BI was believed to be responsible for cholesterol delivery to steroidenic tissues and liver. SR-BI is now known to be the only protein known to be involved in cholesterol transport. The specification exemplifies direct and competitive binding studies for use in the claimed methods as described above. More specific information on screening of patient samples and hybridization probes is provided at pages 40-41 and 43-50.

(6) ISSUES ON APPEAL

The issues presented on appeal are:

(1) whether claims 11-13, 19-22 and 44-50 are enabled under 35 U.S.C. § 112, first paragraph,

(2) whether claims 11-13, 19-22 and 44-50 are adequately described in the specification pursuant to 35 U.S.C. §112, first paragraph;

(2) whether claims 11-13, 19-22 and 44-50 are clear and definite as required by 35 U.S.C. § 112, second paragraph;

(3) whether claims 11, 13, 19, 20 and 22 lack novelty under 35 U.S.C. § 102(a) over Calvo et al., J Biol Chem (1993), 268(25): 18929-18935 ("Calvo"); and

(4) whether claim 21 is obvious under 35 U.S.C. § 103(a) over Calvo et al., J Biol Chem (1993), 268(25): 18929-18935 ("Calvo").

(7) GROUPING OF CLAIMS

Appellants submit that the claims do not stand or fall together.

Claims 11-15 and 19-22 are drawn to an isolated nucleic acid molecule that encodes a type BI scavenger receptor protein, alone or in combination with an expression vector or cell for expression thereof. Claims 14 and 15, which are specific for molecules having SEQ ID NO:3 and 4, respectively, have been allowed. Claim 19 defines a molecule defining a human scavenger receptor protein. Claim 21 defines the molecule in an expression vector. Claim 22 defines the molecule in a host cell.

Claims 44-47 are method claims. Since each method requires different reagents, different method steps, different starting materials, and different motivation to combine as appellants' have done, the method claims must be analyzed separately.

Claims 44-47, drawn to a method for screening for compounds altering binding of LDL or modified LDL to a scavenger receptor protein, which does not require the nucleic acid molecule of claims 11-13 and 19-22.

Claims 44 and 47 are drawn to a method for screening for a compound which alters the binding of scavenger receptor protein type BI as defined by the application. The method involves providing reagents for use in an assay for binding of low density lipoprotein or modified low density lipoprotein to the scavenger receptor protein, adding the compound to be tested to the assay, and then determining if the amount of modified low density lipoprotein or low density lipoprotein which is bound to the scavenger receptor protein is altered as compared to binding in the absence of the compound to be tested.

Claim 45 is drawn to the method of claim 44 but limits the assay for binding to a cell expressing the scavenger receptor protein, *which occur naturally and for which sources are identified in the application.*

Claim 46 is drawn to the method of claim 44 but further limits the compound to one that is selected from a library of compounds by randomly testing for alteration of binding.

Claim 48, drawn to a method for removing LDL from blood by reacting the blood to SR-BI protein, which does not require the nucleic acid molecule of claims 11-15 and 19-22. The blood is reacted with immobilized scavenger receptor protein type BI under conditions wherein the low density lipoprotein is bound to the scavenger receptor.

Claim 49, drawn to a method for inhibiting uptake of lipoprotein or lipids by adipocytes by inhibiting binding of the lipoprotein to the SR-BI, which does not require the nucleic acid

molecule of claims 11-13 and 19-22. The method involves selectively inhibiting binding of lipoprotein to the scavenger receptor protein type BI under conditions wherein the low density lipoprotein is bound to the scavenger receptor.

Claim 50, drawn to a method for screening patients for abnormal scavenger receptor protein or function by determining the presence, quantity or function of the SR-BI and comparing it to that present in normal cells, which does not require the nucleic acid molecule of claims 11-13 and 19-22.

(8) ARGUMENTS

(a) The Claimed Invention

As discussed above under grouping of the claims, the claims are broadly divided into two groups: claims drawn to isolated nucleic acid molecules that code for scavenger receptor proteins that are characterized by a defined binding affinity and methods for screening based on binding of the scavenger receptor proteins. The methods can be further divided based on the reagents and steps by which a particular object is achieved: (1) screening of compounds altering binding of SR-BI to LDL or modified LDL; (2) removing LDL from blood by reacting the blood with immobilized SR-BI; (3) inhibiting uptake of lipoproteins or lipids in adipocytes by inhibiting binding of the LDL to SR-BI; and (4) screening patients for abnormal SR-BI by measuring the amount or function of the SR-BI and comparing it to SR-BI in normal cells.

SR-BI is defined in the specification based on its three dimensional structure (see Figure 1B), amino acid sequence (SEQ ID Nos. 4 and 8), and binding activity (binds native LDL, modified LDL when in the presence of 10% serum, and HDL). It has been demonstrated to be

unique in all three areas, and to exhibit complete identity in three dimensional structure and functional activity across all species and have very high sequence identity between species (see, for example, the printouts of the amino acid sequences for the SR-BI cloned from hamster, rat, mouse, human and cattle, showing the similarity between the proteins, as well as the hamster (SEQ ID NO 4) and murine (SEQ ID NO 8) amino acid sequences provided in the application). Further, from the latter, one can readily determine which amino acids are conserved between species and critical function. Moreover, it is possible to detect SR-BI from one species with the DNA from another. As described in the application, Northern blot analysis of murine tissues was conducted using the hamster DNA), to show that SR-BI is most abundantly expressed in fat and is present at moderate levels in lung and liver. One skilled in the art, reading the phrase "SR-BI" or "scavenger receptor protein type BI" would know that this referred to a very particular type of protein. Based on the tissue expression data in the application, as well as the binding data, one skilled in the art would also know that it is involved in lipid transport, that it is highly unusual because it binds both native and modified LDL, that it binds cholesterol and HDL, and that it plays a role in steroidogenesis and transport of cholesterol to the liver, unlike any other scavenger receptor protein.

SR-BI, and the nucleic acid molecules encoding SR-BI, were not known to exist prior to cloning and expression of the SR-B1 receptor from hamster and then murine cells by appellants. Appellants obtained the DNA encoding the receptor while conducting studies to extend the analysis of the structure and function of mammalian modified lipoprotein scavenger receptors, using standard screening assays for lipoprotein binding by proteins expressed from DNA

obtained from a variant Chinese hamster ovary cell line (Var-261, which also expresses an apparently novel polyanion binding scavenger receptor distinct from SR-BI). Since many proteins are known to bind to lipoproteins, especially modified lipoproteins, the protein obtained from the Chinese hamster ovary cell line was characterized based on its binding specificity and compared to other known receptors, such as SR-A and CD36, a plasma membrane glycoprotein present in a restricted number of cell types, including platelets, monocytes, and some types of endothelial, epithelial, and melanoma cells. Not only is the binding specificity of these two proteins different, the cDNA encoding SR-BI yields a predicted protein sequence of 509 amino acids which is only approximately 30% identical to those of the three previously identified CD36 family members.

SR-BI is an important, highly conserved protein, playing a critical role in cholesterol transport. Once one has the protein and the isolated DNA encoding protein, from any species, it is possible to make antibodies to the protein or hyridization probes which can be used to screen patients or tissues for expression of SR-BI in levels or with function that is not normal (claim 50); it can be used as a target in a screening procedure for drugs which bind to SR-BI to alter lipid or lipoprotein uptake or transport (claims 44-47 and 49); and it can be immobilized and used to remove LDL from a patient's blood (claim 48). None of these methods require any reagents not explicitly described and demonstrated in actual examples in the application.

(b) Rejections Under 35 U.S.C. § 112

i. Rejection of Claims 11-13, 19-22 and 44-50 under 35 U.S.C. § 112, first paragraph (enablement)

The Legal Standard

The Court of Appeals for the Federal Circuit (CAFC) has described the legal standard for enablement under § 112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art, without undue experimentation (*See, e.g., Genentech, Inc. v. Novo Nordisk A/S*, 108 F3d at 165, 42 USPQ2d at 1004 (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also *In re Fisher*, 427 F.2d at 839, 166 USPQ at 24; *United States v. Telectronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988); *In re Stephens*, 529 F.2d 1343 (CCPA 1976)). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (*M.I.T. v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985)). In addition, as affirmed by the Court in *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art.

Whether the disclosure is enabling is a legal conclusion based upon several underlying factual inquiries. See *In re Wands*, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir. 1988). A determination of undue experimentation is a conclusion based on weighing many factors, not just a single factor. Many of these factors have been summarized in *In re Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986) and set forth in *In re Wands*. They are:

(1) The quantity of experimentation necessary (time and expense); (2) The amount of direction or guidance presented; (3) The presence or absence of working examples of the invention; (4) The nature of the invention; (5) The state of the prior art; (6) The relative skill of those in the art; (7) The predictability or unpredictability of the art; and (8) The breadth of the claims.

In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.' *Atlas Powder Co., v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984). There is no requirement for examples.

The Examiner's attention is drawn to the Board of Appeals decision in the parent of this application, U.S.S.N. 08/265,428, which contains no more disclosure than the present application.

The Board begins on page 7 with a discussion of the legal requirements for enablement, noting that the standard is whether one of skill in the art is able to practice the claimed invention at the time the application was filed without undue experimentation, stating in relevant part:

"nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples", quoting from In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971) . The Board then notes that the burden is on the *examiner* to provide a reasonable explanation of why the specification does not enable the claimed invention.

This standard was further clarified by the Court of Appeals for the Federal Circuit in *Amgen, Inc. v. Hoechst Marion Roussel, Inc. and Transkaryotic Therapies, Inc.*, 314 F.3d 1313 (Fed. Cir. 2003). As the Court stated:

> Both the written description and enablement requirements are defined by 35 U.S.C. § 112, first paragraph, which states that the patent specification must contain "a written description of the invention, and of the manner and process of making and using it...[such] as to enable any person of ordinary skill in the art to which it pertains ... to make and use the same ... " The purpose of the written description requirement is to prevent a patentee from later asserting that he invented something which he did not. Thus the patentee must "recount his invention in such detail that his future claims can be determined to be encompassed within his original creation." *Vas- Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1561, 19 U.S.P.Q.2d 1111, 1115 (Fed. Cit 1991). The purpose of the enablement requirement is to teach those or ordinary skill in the art how to make and use the invention without "undue experimentation." The specification does not need to teach what is already known in the art. The specification is enabled if one of ordinary skill in the art only engages in routine experimentation to make the invention.

Claims 11-13 and 19-22 are Enabled by the Specification

Appellants have demonstrated actual reduction to practice in the application as filed (1) isolation of a nucleotide molecule encoding SR-BI from a first species (hamster) and (2)

isolation of a nucleotide molecule encoding SR-BI from a second species (mouse). Appellant's Declarations under 37 C.F.R. 1.131 and 1.132 demonstrates that this information was sufficient to screen data bases to obtain sequence encoding the human analog. In minutes, appellants were able to identify the human sequence using the high degree of homology and conserved sequence between the two species previously isolated and characterized, and that of the human sequence.

Appellants have proven that they enable claims to the nucleotide molecule encoding SR-BI from multiple species and that others could use the same information and techniques to isolate the genomic DNA and polymorphs of the DNA encoding human SR-BI proteins. The examiner has provided no evidence that one skilled in the art would not expect to be able to isolate the homologous nucleotides molecules from any number of other representative widely divergent species.

It is unclear what the basis of the rejection is, other than that the claims are clearly intended to encompass the genus of nucleotide molecules encoding SR-BI, defined in terms of its primary (amino acid sequence) and secondary structure (Figure 1B) as well as functional activity (binding). Attention is drawn to appellants' declaration under 37 C.F.R. 1.132 in support of enablement. These statements must be considered absent actual evidence, not mere conjecture or argument, to the contrary. The examiner has apparently ignored the explanation and evidence provided for how one can isolate a genomic DNA using a cDNA. It was routine to screen genomic libraries using cDNA hybridization probes at the time of filing the present application (see Exhibits 6-8, submitted with the declaration under 37 C.F.R. 1.132). The hybridization conditions such as temperature and salt concentration can be adjusted to decrease the stringency

of the probe hybridization. A lower stringency condition would allow for a probe to bind sequences that were very similar but not identical to the cDNA probe. This would be ideal for screening genomic libraries from different species for homologous sequences. Additional proof of this is shown by reference to U.S. Patent No. 5,998,141 to Acton, which the Board cited in its decision in this case. cDNA encoding SR-BI, just as appellants describe in their application, was not only used to isolate the genomic DNA encoding SR-BI, but also polymorphic variations. See example 1, beginning at col. 32, line 54. See also col. 17, lines 8-38, stating that the same hybridization conditions were used, and can be used, to isolate genomic DNA encoding SR-BI from different species and including polymorphs or allelic variations. Accordingly, the examiner's statements to the contrary are simply wrong.

One of skill in the art would have known in 1994 how to make, or obtain, a human genomic library and synthesize a radiolabeled cDNA probe with routine experimentation. Probing nitrocellulose filters with the radiolabeled cDNA probe was already established and widely used in the art. These techniques were established and used routinely for at least 10 years prior to the filing of this application. Therefore one could isolate either genomic DNA or DNA encoding polymorphs, as defined by the claims, with only routine experimentation.

The specification provides a clear and enabling disclosure of these methods. The previously submitted declaration under 37 C.F.R. 1.132 referred to specific passages in the specification wherein general methods using nucleic acid probes to isolate genomic DNA sequences *via* libraries (page 10, lines 2-20); using nucleic acid probes (page 25, lines 10-20); and making genomic libraries (paragraph bridging pages 34 and 35) are all described.

Furthermore, the specification provides sufficient guidance for one skilled in the art to make and use a functional scavenger receptor encoded by the nucleic acid molecule of claim 11. As defined by claim 11, the receptor's functionality is centered on binding to 1) LDL, or 2) modified liproprotein having the characteristics of acetylated low density lipoprotein, in cell medium containing 10% serum. Appellants have clearly demonstrated that this screening method is routine by expressing both cDNAs and showing the binding of the SR-BI encoded thereby, using standard binding assays. That is all that is legally required. Page 40, lines 14-16, states that one would *typically* screen for expression of *functional* receptor. Pages 16 and 17 describe well known methods used for measuring receptor binding (and uptake and degradation). Such methods were well described in references dating back to 1983 and 1991 (Krieger and Freeman; see lines 8 and 9 of page 16). The *in vitro* binding activity of SR-BI is shown in Figures 2A,B and C, 3A and 3B, 5, 6, and 7. The *in vitro* binding specificity is compared to CD36 in Figures 4A, B and 5. This in combination with the materials and methods described in the application are clearly enabling to show the function of SR-BI. The *in vivo* function in the binding of cholesteryl esters in HDL is shown in Figure 8A, B and also described, and shown diagramatically in Figure 9.

The examiner's statements that the structure of SR-BI is not defined are absurd - the nucleotide sequence defines specific amino acid sequence. The tertiary structure of the protein encoded by this amino acid sequence is shown in Figure 1B. Moreover, the claims drawn to the protein, and variants thereof, have been allowed and issued as a U.S. Patent in the parent application, following appeal to the Board of Appeals.

The claims do not mention SEQ ID NO:4 or SEQ ID NO:8. The claims are directed to nucleic acid molecules encoding a functional scavenger receptor protein type BI. The terms "SEQ ID NO:4" and "SEQ ID NO:8" are nowhere to be found in the pending claims. As stated above, the claims are directed to *nucleic acid molecules* encoding a functional scavenger receptor protein type BI. Moderately stringent hybridization conditions (at a temperature of approximately 25°C below the melting temperature of a perfectly base-paired double-stranded DNA molecule, which one of ordinary skill in the art would know would consist of SEQ ID NO:3 or SEQ ID NO:7, just as the examiner has noted) allows for some variation in the nucleic acid sequence. However, the extent of this variation is precluded by the fact that what is encoded must be a receptor that binds to LDL or modified lipoprotein under the conditions defined by the claim.

In quoting the M.P.E.P §2164.08(a), the Examiner appears to be confusing structure (means) and the stated property (function) in the present claims. SEQ ID NO:3 and SEQ ID NO:7 are the two structural means used in defining the claimed nucleic acid molecules. These structural means, coupled with the explicitly stated stringency conditions in combination with the encoded amino acid sequence have the defined function and structure shown in Figure 1B, are all that is required to clearly define the claimed nucleic acid molecules. It is worthwhile to note that the claimed nucleic acids bind to SEQ ID NO:3 or SEQ ID NO:7 by virtue of their chemical structure *which is complementary* to the chemical structure of the target sequence. Antigen is also bound by antibodies by virtue of their chemical structure which is complementary to the chemical structure of the antibodies. *The structure is not complementary in the sense that one*

strand of DNA binds to a complementary strand of DNA, but complementary in that the three dimensional structure as well as the chemical composition is complementary to the three dimensional structure and chemical composition of the target sequence.

Claim 19 is dependent from claim 11. As such, it is necessary for the claimed molecule to hybridize to SEQ ID NO:3 and SEQ ID NO:7 under moderately stringent hybridization conditions. In view of the present specification and what was known in the art at the time of filing the present specification (as discussed in the foregoing paragraphs), one of ordinary skill would realize that trial and error experimentation is not a requisite for isolating the molecule of claim 11 or claim 19. Indeed, **Appellants were able to use SEQ ID NO:3 to isolate SEQ ID NO:7 and their sequences to identify the human sequence from an available data base (See Krieger and Action declaration).** The claims do not make reference to "non-rodent" species. Either of SEQ ID NO:3 and SEQ ID NO:7 and an available library is all that is required, under moderately stringent conditions, to give structure to the claimed molecule. The Examiner even admits on page 21 of the Office Action mailed August 6, 2003 that one of skill in the art would reasonably predict that these sequences exist in different species.

In response to the Examiner's comments regarding P1-established libraries and cloning genes using cDNA, appellants have submitted a copy of Yang *et al.* (*Proc. Natl. Acad. Sci.* USA, Vol. 87, pp 7907-7911, 1990) clearly demonstrating that the technique of using recombinant phage for the purpose of library screening was well-established by 1990. Furthermore, Southern hybridization and restriction fragment length polymorphism (RFLP) analyses were commonly used techniques at the time of filing the present application (for example, see body of Yang *et*

al.). Two abstracts were also previously submitted (Rouleau *et al.*, *Genomics*, **1989**, 4(1):1-6; and Ioannou *et al.*, *Nat. Genet.* **1994**,6(1):84-9), illustrating the use of recombinant phage libraries enriched for human chromosome 22 sequences for use in RFLP analysis and P1 vectors for introducing recombinant DNA into *E. coli*, respectively. Using cDNA to aid in cloning entire genes would not have been undue at the time of filing the present application. Furthermore, chromosomal walking was a routine method used to clone many genes at the time of filing the application. The *application* of each *well known* technique to the particular situation that the researcher has carved out for him-/herself was routine. The examiner has admitted that library screening using probes from cDNA was routine (see page 16 of the office action mailed on August 6, 2003).

With respect to administration of compounds to block binding, attention is drawn to the examples and graphs showing inhibition of binding to the SR-BI. It is believed these *actual examples* fully demonstrate the use of compounds to inhibit SR-BI binding as claimed.

Lastly, once one has the SR-BI protein and/or the DNA encoding SR-BI, from any species, it is possible to make antibodies to the protein or hybridization probes which can be used to screen patients or tissues for expression of SR-BI in levels or with function that is not normal (claim 50); it can be used as a target in a screening procedure for drugs which bind to SR-BI to alter lipid or lipoprotein uptake or transport (claims 44-47 and 49); and it can be immobilized and used to remove LDL from a patient's blood (claim 48). None of these methods require any reagents not explicitly described and demonstrated in actual examples in the application.

In summary, one skilled in the art to which claims 11-13 and 19-22 pertain, cloning of a scavenger receptor protein, would have been able to obtain a nucleotide molecule encoding human SR-BI with no more than routine experimentation, as of the priority date of this application (June 23, 1994), based on the disclosure by appellants using commercially available reagents and standard techniques.

While it is true that the specificity of nucleic acid interaction, or hybridization, can be affected by the conditions that the hybridization occurs under, those of skill in the art know how to perform hybridization experiments that lead to specific gene recognition of homologues, and the present application **specifically describes** how to do this for a SR-B1 cDNA. For example, on page 18, line 27 to page 19, line 6, there is an explicit description of a hybridization procedure in which the isolated hamster SR-B1 cDNA is used to produce a 600 base probe (derived from a BamHI restriction digest of the DNA shown in SEQ ID No. 3) which is used to probe different cell types from murine tissues and from 3T3 cells. The hybridization and washing conditions were done at 42° C and 50° C respectively using the well known conditions described by Charron et al. *Proc. Natl. Acad. Sci.* 86 2535-2539 (1989). Performing the hybridization analysis as described in the application clearly shows that a single predominant band of 2.4 kb was abundant in fat and present in moderate levels in lung and liver (page 31:line 11 to page 32:line 24). While the 600 base probe derived from the hamster scavenger receptor type B1 cDNA hybridizes as a single gene sequence in mouse, a probe from CD36 has a different hybridization pattern, indicating that the hybridization assay described is sufficient to differentiate between CD36 and Appellants' nucleic acids encoding SR-B1 type proteins. This fact is significant since, as pointed

out by the Examiner, other non-SR-BI genes are closely related in sequence to hamster and human SR-BI sequence (see Calvo et al.). This indicates that while CD36 and SR-B1 are related proteins (both members of the CD36 superfamily), they are not so related as to be considered homologues with each other and one skilled in the art would not interpret a reference to SR-BI as being the same as a reference to CD36. CD36 is also excluded from the scope of the claims due to the binding specificity requirement: as shown in Figure 5, graphing competitive binding of acetylated LDL to either SR-BI or CD36 in the presence of native LDL, SR-BI binds native LDL and CD36 does not.

In summary, one skilled in the art, reading the claim which includes not only the phrase "hybridization" in conjunction with a defined sequence as well as the functional activity ("binding specificity") of the SR-BI would know exactly what was defined by the claims. The claims are therefore definite, and enabled, by the specification.

Claims 11-13, 15, 19-22 were also rejected under §112, first paragraph, on the basis that the "claims encompass nucleic acids encoding proteins whose amino acid sequences have been substantially altered from their natural forms whereas the instant specification does not provide the guidance that is required to produce such nucleic acids in a predictable manner."

First, its should be noted that the mere fact that claims encompass embodiments that are not explicitly described, nor exemplified, does not render the claims non-enabled. In fact, inclusion of some embodiments that are even inoperative would still not render the claims non-enabled.

As articulated by this Board in *Ex parte Mark*, 12 U.S.P.Q.2d 1904 (Bd. Pat. App. & Int'f 1989), "When it is considered that the claims remaining on appeal all require that the mutein produced retain the biological activity of the native protein, we consider the disclosure of this application to be enabling . . . The fact that a given protein may not be amenable for use in the present invention in that the cystein residues are needed for the biological activity of the protein does not militate against a conclusion of enablement. One skilled in the art is clearly enabled to perform such work as needed to determine whether the cysteine residues of a give protein are needed for retention of biological activity." 12 U.S.P.Q.2d at 1906-1907.

As applied to the claims here on appeal, one skilled in the art can obtain starting material merely by reference to the application before him. He can readily compare the amino acid sequences for the hamster and mouse SR-BI proteins and determine which amino acids are conserved and which are not. He can enter the amino acid sequence into computer programs that were commercially available in 1994 and look at the resulting structure, to determine which amino acids are located at critical regions. Even if an amino acid is changed, intentionally or accidentally or by nature, it would require no more than routine effort to screen for activity. The assays to screen for binding activity are detailed in the application and the expected ranges actually demonstrated. The minimal nature of the experimentation required to obtain these proteins is demonstrated by how appellants, with no knowledge of the existence of this protein nor its activity, were able to screen *an entire expression library* for activity, as they did to originally isolate the SR-BI from hamster cells. See in particular the studies reported at page 36, in which *3500 clones were screened initially for activity, then subdivided into 18 subpools of 350*

clones which were transfected into cells and screened again. Appellants also demonstrated that they were able to obtain the mouse SR-BI DNA using the hamster DNA, with no more than routine effort. With the sequences of SR-BI proteins from two different species, and their activity profiles in hand, as well as the requirement that the nucleic acid hybridize to these known sequences, and encode a protein having the structure as shown in Figure 1B (i.e, encode a scavenger receptor BI protein), it would only require routine testing to determine which molecules are encompassed by the claims.

The CCPA first addressed the issue of protein variants in *In re Fisher*, 427 F.2d 833 (CCPA, 1970). Integral to this holding was the court's reliance on the knowledge of one of ordinary skill in the art, and the lack of a showing that one of ordinary skill in the art could obtain sequences other than 39 amino acids long. The court stated,

> The parent specification does not enable one skilled in the art to make or obtain ACTHs with other than 39 amino acids in the chain, and *there has been no showing that one of ordinary skill would have known how to make or obtain such other ACTHs without undue experimentation.* As for Appellant's conclusion that the 25th to 39th acids in the chain are unnecessary, *it is one thing to make such a statement when persons skilled in the art are able to make or obtain ACTH having other than 39 amino acids*; it is quite another thing when they are not able to do so.
>
> Id. at 836. (emphasis added).

It is clear that the court was placing great emphasis on what one of ordinary skill in the art could have hoped to make or obtain. This decision was handed down in 1970, on an application filed November 29, 1960, claiming priority from an application filed June 9, 1954. The priority application was filed one year after Watson and Crick determined that the structure of DNA was a double helix (Watson and Crick *Nature* 171, 964-967 (1953)). It would still take seven years of research before scientists even knew that there was a triplet code between a DNA sequence and a protein sequence (Crick et al. *Nature* 192 1227-1232 (1961)). It is not reasonable to assume that a holding, based on an application filed in 1954, prior to the advent of biotechnology, is controlling on biotechnology itself. The court in *In re Fisher* very likely correctly held that "one could not make or obtain", without undue experimentation, a protein with less than 39 amino acids . . . *in 1954*. The court just as correctly noted though that if one of ordinary skill in the art could have made or obtained such a protein then the holding would have been very different. *Unlike this case*, appellants have demonstrated that one of ordinary skill in the art of cloning *in 1994* can obtain other nucleotide molecules encoding SR-BI with the requisite activity, without undue experimentation.

The court in *Amgen, inc. v. Chugai Pharmaceutical Co., LTD.*, 927 F.2d 1200 (Fed. Cir. 1991) relied heavily on the holding in *In re Fisher* to find a claim drawn to a large number of non-natural Erythropoietin (EPO) analogs invalid for failing to meet the requirements of 35 U.S.C. 112. The court focused on the number of possible analogs that were encompassed by the claim **and** on the uncertainty held by the Appellant as to which analogs, already produced, possessed the activity. The trial court relied on expert testimony which provided that "Amgen is

still unable to specify which analogs have the biological properties set forth in the claim." *Id.* at 1213. The Federal Circuit chose to focus on the making and using of the DNA sequences, which produce the protein which has the biological activity, rather than the biological activity itself. While the *Amgen* court spoke positively of *In re Angstadt*, 537 F.2d 498, 502, which held that it is not necessary that a patent Appellant test all embodiments of his invention, just that he provide a sufficient disclosure to enable one skilled in the art to practice the full scope of the claims, they stated that for claims based on DNA sequences a sufficient disclosure meant, "disclosing how to make and use enough sequences to justify grant of the claims sought." *Id.* at 1213. The court went on to state, "what is relevant *depends on the facts*, and the facts here are that Amgen has not enabled *preparation of DNA sequences* sufficient to support its all-encompassing claims." *Id.* at 1213. (emphasis added). Again, as in *In re Fisher*, the focus is on what Appellants, or one of ordinary skill in the art, could do. The court focused on whether the preparation of the DNA sequences, within the scope of the claims, could *be prepared.* The application at issue was filed on November 30, 1984 and claimed priority to an application filed on December 13, 1983. Therefore, the "facts" relevant to the "preparation of DNA sequences" in the courts mind were those that existed in 1983. This is almost four years prior to the advent of PCR. Chemical synthesis of DNA was still only able to routinely produce short oligonucleotides. In short, the two most important technological advances for the "preparation of DNA sequences" in a manner without "undue experimentation", PCR and highly efficient automated DNA synthesis, were still years away. A case decided based on the level of skill in the art *ten years earlier*, in a field

changing almost hourly, cannot be used as a basis for a determination of what one skilled in the art would do as of 1994.

In *Hormone Research Foundation v. Genentech, Inc.* 904 F.2d 1558, 1568-69 (Fed. Cir. 1990), the court reversed a summary judgement for lack of enablement regarding claims directed to human growth hormone. The lower court had ruled that the alleged infringer had presented sufficient evidence indicating that the application was not enabled to merit summary judgement. (*Hormone Research Foundation v. Genentech, Inc.*, 708 F.Supp 1096 (N.D.Cal. 1988). The Federal Circuit remanded this issue for further adjudication because the lower court had failed to adequately address the analysis of *In re Hogan*, 559 F.2d 959 (CCPA 1977) and *United States Steel Corp. v. Phillips Petroleum Co.* 865 F.2d 1247 (Fed. Cir. 1989). In commenting on the relevance of these cases the *Hormone Research Foundation* court stated,

> It is unclear whether the high degree of potency and purity contemplated by the district court's analysis of enablement was influenced by the *potency and purity obtainable through recombinant DNA methodology.* Moreover, it is unclear from the record before us *whether that technology existed at the time the application was filed.* Further factual development as to the *state of the art at the date of the application* . . . is required for this court to review the enablement issues.
>
> *Id.* at 1568-1569. (emphasis added).

The meaning and intent of the court is clear: one must assess the question of enablement in the light of the knowledge of one of ordinary skill in the art *at the time the application is filed.* In this case, Appellants have demonstrated one can obtain and screen huge numbers of molecules rapidly and without experimentation, and that it is possible to routinely obtain additional molecules encoding SR-BI merely by hybridization to one of the disclosed nucleotide molecules.

A central issue in the above cases is the level of predictability in the art. The question remains, however, as to what "unpredictability" means. For example, the court in *In re Vaeck* 947 F.2d 497 (Fed. Cir 1991) addressed the issue of unpredictability by stating, "we do *not* imply that patent applications in art areas currently denominated as unpredictable must never be allowed generic claims encompassing more than the particular species disclosed in their specification." *Id.* at 496. (emphasis contained in original). The court went on to state that "there must be sufficient disclosure . . . to teach those of ordinary skill how to make and how to use the invention . . ." *Id.* at 496. The question remains, what is a sufficient disclosure for an application that is in an "unpredictable" art? The clear answer given by the court was "the disclosure must adequately guide the art worker to determine, *without undue experimentation*, which species among all those encompassed by the claimed genus possess the disclosed utility. *Id.* at 496. (emphasis added). The court did **not** state, "without any experimentation," they stated "without undue experimentation". This means that a standard of "predictability" that excludes "all" experimentation is simply incorrect.

"Unpredictability" is often used as a sword by the PTO to slash the scope of a legitimate biotechnology claim. The sharpness and size of this sword, however, are unduly exaggerated

because of the misapplication of what is and should be "predictable". In the area of functional variants, such as discussed in *In re Fisher* or *Amgen Inc., v. Chugai Pharmaceutical Co.,* the standard when assessing whether the specification enables one of ordinary skill in the art to make and use the claimed variants is whether it would require "undue experimentation" to determine which variants are functional. In the language of *In re Vaeck*, "the disclosure must adequately guide the art worker to determine, *without undue experimentation*, which species among all those encompassed by the claimed genus possess the disclosed utility. *Id.* at 496.

The priority date for the application on appeal is June 23, 1994. By this time technologies such as PCR were highly developed and were routinely utilized to "prepare" DNA molecules which encoded for variants of known protein sequences. The importance of utilizing PCR cannot be overestimated with respect to the manipulation of DNA molecules, and specifically the insertion, deletion or substitution of DNA sequences which lead to changes in the amino acid sequence of a protein. The specification contains ample description of recombinant DNA methods that enable one of ordinary skill in the art to make SR-B1 receptors with varied amino acids. For example, on page 51 the subsection entitled "Preparation of Receptor Protein Fragments" describes numerous methods including cleaving the protein with various proteases, expression of the altered protein from a recombinant DNA molecule, and even chemical synthesis of the desired protein fragment. On page 52:lines 14-18 the specification states, "These methods can be used to synthesize peptides having identical sequence to the receptor proteins described herein, or substitutions or additions of amino acids, which can be screened for activity."

The "preparation of the DNA molecules" encoding the variants of the sequences disclosed in SEQ ID NOs. 4 and 8 are fully enabled by the specification. Likewise, the assays to determine those variants that have the desired activity are readily described. The claims require that the nucleic acids encoding the SR-B1 receptor are capable of hybridizing with either SEQ ID. Nos. 3 or 7, and that they encoding proteins selectively binding to low density lipoprotein and modified lipoprotein. Assays for determining whether the modified DNA molecules hybridize to SEQ ID Nos. 3 or 7 are described at least from page 18:line 27 to page 19:line 6. As is indicated in these pages these methods were published in 1992, approximately three years before the priority date of the application. Clearly one of ordinary skill in the art would be able to practice techniques that were nearly three years old. In addition the application describes a number of assays that indicate whether a candidate SR-B1 protein binds low density lipoprotein and modified lipoprotein as required by the claims. For example, on page 19 there is a subsection entitled "HDL Binding Studies" and following this section is the description of "Phospholipid Binding and Competition Assays." On page 21 there is yet another section entitled "Ligand Binding Assays" that discloses methods for determining if various low density lipoproteins and modified lipoproteins bind cells containing candidate SR-B1 receptors.

The Examiner is clearly falling into the trap of interpreting "predictability" as prediction without **any** experimentation. This standard is absolutely inconsistent with the standard of "undue experimentation" set up in *In re Forman* and reiterated in *In re Wands*. The very word "predictability" is one of the factors to *determine* whether undue experimentation exists, not whether *any* experimentation should be commenced at all. It is a misapplication of the *Wands*

standard to first ask the question "is it predictable which variant *a priori* has activity?", and then if the answer from the Examiner's position is "no" to forgo the undue experimentation analysis. This is clearly putting the proverbial cart before the horse. As Judge Rich illustrated in *In re Vaeck*, "the disclosure must adequately guide the art worker to determine, *without undue experimentation*, which species among all those encompassed by the claimed genus possess the disclosed utility. *Id.* at 496. Clearly, "predictability" does not supercede the standard of "undue experimentation" and the making of a DNA molecule encoding a variant of a SR-B1 receptor and testing this receptor for activity and characteristics required by the claims, in the technological world of 1994 is **not** undue experimentation.

The requirement by the Examiner that the specification contain working examples misconstrues the law and misconstrues the facts of the application. The legal standard does not require "working examples" in the specification, it is merely one of the factors which may be considered in a determination of undue experimentation. On page 5 of the Advisory Action mailed August 3, 1998, the Examiner states, "*Wands* now requires that one consider the number of working examples presented in the instant specification." This is false. The Federal Circuit explicitly stated in *Amgen, inc. v. Chugai Pharmaceutical Co., LTD.*, "it is not necessary that a court review all the *Wands* factors to find a disclosure enabling" *Id.* at 1213. Thus, the specification does not require working examples to meet the correct standard which is undue experimentation.

Notwithstanding the above, the specification does provide working examples showing the isolation and characterization of nucleotide molecules encoding SR-B1 proteins having different

amino acid sequences that meet all of the requirements of the claims, the hamster homologue of SR-B1 and the murine homologue of SR-B1. While the Appellants have not described in the application making "synthetic" variants of the SR-B1 protein, nature has provided the necessary evidence that there are protein variants of the hamster SR-B1 that exist which meet the limitations of the claims. There are numerous positions in the amino acid sequence of the murine homologue to the hamster SR-B1 that are "variant" from the hamster SR-B1 sequence. The application teaches one how to make the protein variants, the application teaches one how to test the protein variants for activity, and the application teaches one that not every amino acid is required for function as required by the claims. The latter demonstration is what a working example can provide for an application, and this demonstration is provided by the fact that multiple homologues are disclosed.

The *Wands* factors do not require the "making of record prior art" as indicated by the Examiner at page 3 of the Advisory Action mailed on August 3, 1998. First, it is not required that all of the *Wands* factors be addressed to find that a claim does not require undue experimentation. Second, "making art of record" is not even one of the specific factors suggested. The nearest suggested analysis is "the state of the prior art." There is no requirement that all which is known to one of ordinary skill in the art be submitted to the Patent Office either in the form of the specification or in the art made of record.

Notwithstanding the above, the prior art made of record, while not explicitly required by the *Wands* factors, clearly supports the enablement of protein variants. For example, Cullen et al, "Use of Eukaryotic Expression Technology in the Functional Analysis of Cloned Genes,"

Methods in Enz. 152:684-704 (1987) describes numerous methods for producing eukaryotic expression vectors, such as those used in the present specification, to test specific DNA sequences for activity. Methods for domain swapping and protein mutagenesis were readily known to those of ordinary skill in the art and this is exemplified by Daugherty, et al., "Polymerase chain reaction facilitates the cloning, CDR-grafting and rapid expression of a murine monoclonal antibody directed against the CD18 component of leukocyte integrins," *Nucl. Acids Res.* 19:2471-2476 (1991).and Itakura et al., "Synthesis and use of synthetic oligonucleotides," *Ann. Rev. Biochem.* 53:323-356 (1984). Daugherty et al. describes methods for using the Polymerase Chain Reaction (PCR) to swap functional domains of a specific antibody between the murine and human homologues. Itakura et al. actually discusses site mutagenesis prior to PCR and describes this technology, in 1984, by saying "The once seemingly obvious limitations of this technique [referring to site directed mutagenesis] –availability of synthetic DNA and a knowledge of the nucleotide sequence of the target region—are no longer major factors." *Id.* at 343-344. Thus, in 1984, 10 years before the priority date of this application, the opinion of those of ordinary skill in the art was that the factors which arguably caused undue experimentation to make protein variants prior to 1984, "are no longer major factors" after 1984.

iii. Claims 44-50 are enabled

As discussed above, claims 44-50 are distinct from the claims drawn to nucleotide molecules. Each of these methods can be performed as described in the application as originally filed, without preparation of any nucleotide molecules encoding an SR-BI other than those explicitly exemplified.

The claimed methods in conjunction with the specification are absolutely clear and complete. One of skill in the art would be able to practice, without undue experimentation, the claimed methods. For example, the Examiner has singled out the recitation of "providing reagents for use in an assay for binding" in claim 44, as incomplete. The specification provides numerous examples of reagents for binding, such as AcLDL and M-BSA to name two. Page 28:line 15 to page 31:line 10 provides an extensive description of binding assays and binding reagents. Claims 44-50 are complete in their recitation of the necessary steps which set out the claimed methods. As outlined in *In re Miller*, 441 F.2d 689, 169 USPQ 597 (CCPA 1971), the breadth of a claim is not to be equated with indefiniteness.

a. Claims 44 and 47 are fully enabled

Claims 44 and 47 are fully enabled by the specification and separately patentable. Claims 44 and 47 are drawn to methods for screening for compounds which alter the binding of the low density lipoproteins to the SR-B1 receptor. *These are not drawn to the compounds themselves.* The method comprises the steps of providing reagents for binding assays of low density or modified low density lipoproteins, adding the compound to be tested, and determining if the amount of low density or modified low density lipoprotein binding to SR-B1 is altered. The specification provides ample support for this method on pages 43 to 51.

b. Claim 45 is fully enabled

Claim 45 is fully enabled by the specification and is separately patentable. Claim 45 is drawn to the methods of claim 44 with the further limitation of requiring the assay include expression of the scavenger receptor protein in a cell, where the inhibiting molecule is a nucleic

acid which alters expression of the scavenger receptor protein. On page 47, a section entitled, "Generation of nucleic acid regulators" describes methods to design and isolate nucleic acid molecules which inhibit the expression of a variety of proteins, including scavenger receptors.

c. Claim 46 is fully enabled

Claim 46 is separately patentable and fully enabled by the specification. Claim 46 is drawn to the method of claim 44 wherein the compounds tested are selected from a randomly screened library. This further limitation of the claim is fully supported in the application at page 45:lines 23-40. *In vitro* selection technologies and combinatorial chemistry approaches to the isolation of small molecule inhibitors are well known, and fully applicable to the isolation of molecules that inhibit SR-B1 binding to low density or modified low density lipoprotein.

d. Claim 48 is fully enabled

Claim 48 is fully enabled by the specification and is separately patentable. Claim 48 is drawn to the screening of patient blood samples and the removal of low density and modified low density lipoprotein from patient blood samples. Support for the limitations of this claim can be found on page 54:lines 9-15. Methods of attaching proteins to solid supports are described and well understood by those of ordinary skill in the art.

e. Claim 49 is fully enabled

Claim 49 was rejected under 35 U.S.C. §112, first paragraph, as allegedly not enabled by the specification. This rejection is solely based on the "intended use" of the claimed compositions. The Examiner has asserted that the specification fails to teach how to "use" the claimed compositions. This rejection was made under 35 U.S.C. § 112, first paragraph, but

really is nothing more than a rejection for lack of utility under 35 U.S.C. § 101. The claimed compositions and methods are fully enabled to make and use as required under 35 U.S.C. § 112, and have more than enough utility to meet the minimal standard required by the judicial interpretation of the utility requirement.

f. Claim 50 is fully enabled

Claim 50 is fully enabled and separately patentable. Claim 50 is drawn to a method of screening patients to determine if the patients have abnormal levels of SR-B1 receptor or abnormally functioning receptor. The method comprises determining if there is a scavenger receptor present that hybridizes to either SEQ ID NOs. 3 or 7 and binds low density or modified low density lipoprotein, and then determining if the quantity present is similar to normal cells and if the function of the SR-B1 receptor is similar to the SR-B1 receptors of normal cells. There are numerous assays for determining the amount of SR-B1 receptor present in a given cell. For example, from page 32:line 25 to page 33:line 5, methods using antibodies to recognize SR-B1 receptors are described. Those of ordinary skill in the art would readily know how to compare the amounts of SR-B1 protein in control cells to the cells of choice using these type of blotting techniques. The application also describes numerous binding assays to various low density and modified low density lipoproteins that characterizes SR-B1 function. One of ordinary skill in the art would know how to compare the binding capabilities of the control SR-B1 and the SR-B1 derived from the specific cell or patient being screened. Claim 50 is fully enabled, and therefore, should be found valid by the Appeal Board.

ii. Rejection of Claim 19 under 35 U.S.C. § 112, first paragraph (written description)

The Legal Standard

Both the written description and enablement requirements are defined by 35 U.S.C. § 112, first paragraph, which states that the patent specification must contain "a written description of the invention, and of the manner and process of making and using it...[such] as to enable any person of ordinary skill in the art to which it pertains ... to make and use the same ... " The purpose of the written description requirement is to prevent a patentee from later asserting that he invented something which he did not. Thus the patentee must "recount his invention in such detail that his future claims can be determined to be encompassed within his original creation." *Vas- Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1561, 19 U.S.P.Q.2d 1111, 1115 (Fed. Cit 1991).

For many years the leading case for the written description requirement in the biotechnology and pharmaceutical arts was *Eli Lilly v. Univ. of Calif. Board of Regents*, in *Regents of University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997), *cert denied*, 523 U.S. 1089 (1998). The Federal Circuit evaluated whether claims to recombinant production of human insulin in U.S. Patent No. 4,652,525 met the written description requirement. The court determined that the specification failed to comply with the written description requirement for only disclosing a single species of DNA encoding non-human insulin.

The Federal Circuit has since held that that the written description requirement can be met by a functional description of claimed materials, if coupled with a known or disclosed

correlation between function and structure. *Enzo Biochem, Inc., v. Gen-Probe, Inc.*, 296 F.3d 1316, 63 U.S.P.Q.2d 1609 (Fed. Cir.2002) ("*Enzo II*"). *Enzo II* states "the written description requirement to be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ... i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." This standard was subsequently affirmed and clarifed in the decision of *Amgen Inc. v. Hoechst Marion Roussel, Inc. and Transkaryotic Therapies, Inc.* 314 F.3d 1313, 65 USPQ 2d (Fed. Cir. 2003).

Claims 11-13, 19-22 meet the written description requirement

The rejected claims define nucleotide sequences by virtue of hybridization to listed nucleotide sequences, as well as by the amino acids which they encode that must form a structure as shown in Figure 1B, having the claimed activity. Appellants have provided the sequences to which the claimed nucleotides must hybridize, as well as the conditions, the three dimensional structure and the function. These features fully define the claimed nucleotide molecules. It is well established at this point that once one provides the structure and function, and has reduced to practice representative species of a genus (two in this case), one has complied with the written description requirements for the genus.

Furthermore, the issue of description is adequately met simply by constructively reducing the material to practice (*Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 19 USPQ2d 1111 (Fed. Cir. 1991)). The Court in *Vas-Cath Inc. v. Mahurkar* stated, "Whether the disclosure of the

application relied upon reasonably conveys to the skilled artisan that the inventor had possession at the that time [i.e., when the application was filed] of the later claimed subject matter." As long as the subject matter was described in the specification as it was claimed, the description requirement is met. Applying this standard, the human homologue as claimed in claim 19 clearly meets the description requirement.

Claim 19 defines a nucleotide molecule encoding a human SR-BI. Appellants acknowledge that the exact nucleotide sequence for this molecule is not recited in the application. However, while the examiner goes into a great deal of discussion regarding issues of species versus genus, acknowledging that Appellants have disclosed a species (actually two, the species from hamster and the species from mouse), he states at page 3 of the Office Action mailed March 19, 1998, that "Because the instant application does not provide a written description of those material properties which distinguish "a human scavenger receptor" from any other mammalian scavenger receptor, a practitioner of the art cannot produce the claimed nucleic acid to the exclusion of a nucleic acid encoding any other mammalian scavenger receptor." This statement is patently incorrect and nonsensical.

First, appellants are not claiming any human scavenger receptor; they are only claiming SR-BI, which is characterized as having a defined structure, amino acid sequence as found in two different species, increased expression in certain types of cells, and a unique binding activity. No other scavenger receptor binds both native and acetylated LDL. No other scavenger receptor binding both native and acetylated LDL can be obtained by routine screening of tissues using a probe from either of the two nucleotide sequences from hamster and mouse that are

provided. Appellants also provide two nucleotide molecules encoding SR-BI and which are complementary to the nucleotide molecule encoding human SR-BI under defined conditions. Appellants demonstrate that it is possible to use a probe from one species to identify DNA encoding the same protein from a second species, as discussed above. Appellants were able to identify the actual human sequence from a data base using the murine and hamster sequences. There are no unique features of human SR-BI that makes it necessary to define human SR-BI any differently than for any other species, other than there are a few nucleotides differences. Indeed, as demonstrated from abstracts from a few subsequently published papers, the human SR-BI is extremely similar in amino acid sequence and identical in binding activity, binding both native and acetylated LDL, which appellants have demonstrated can be routinely used to obtain DNA encoding an SR-BI protein from species other than the species for which nucleotide sequence is known.

In so far as the Examiner is relying on *Regents of the University of California v. Eli Lilly and Company*, 43 USPQ2d. 1398 (CAFC 1997) as the basis for this rejection, Appellants note that *Regents of U.C.* is not applicable since the claims and underlying specification here are not analogous to the facts there. The Court in *Regents of U.C.* relied on the fact that the description of example 6 in the patent at issue prophetically described obtaining a cDNA sequence from the **protein** sequence of the human protein. This is completely different than the situation here, where the specification relies on the use of the homologous cDNA as a probe, not a degenerate sequence obtained by reverse translation of a protein sequence. This difference is absolutely critical because the court in *Regents of U.C.* relied on their own precedence of *In re Deuel* 51

F.3d 1552, 1558, 34 USPQ2d 1210, 1215 (1995). The court stated, "A prior art disclosure of the **amino acid sequence** of a protein does not necessarily render particular DNA molecules encoding the protein obvious because the redundancy of the genetic code permits one to hypothesize an enormous number of DNA sequences encoding for the protein." In relying on the relationship of amino acid sequence to nucleic acid sequence, *Regents of U.C.* is limited to protein-to-DNA situations. It should be noted that the court in *Regents of U.C.* did not specifically address (and thus, did not overrule) the standard that has been accepted for the description requirement for the last 125 years, most recently explicated in *Vas-Cath Inc. v Mahurkar*. Notwithstanding the above, it is noted that only decisions handed down by an *en banc* panel of the Federal Circuit are sufficient to overrule previous case law. In this respect, the decisions of the Federal Circuit in *Eli Lilly* and its progenitor cases do not overrule the longstanding positions taken by the courts on the description requirements. (*Vas-Cath Inc. v Mahurkar).*

Claims 44-50 meet the written description requirement

a. Claims 44 and 47 meet the written description requirement

Claims 44 and 47 are fully supported by the specification and separately patentable. Claims 44 and 47 are drawn to methods for screening for compounds which alter the binding of the low density lipoproteins to the SR-B1 receptor. *These are not drawn to the compounds themselves.* The method comprises the steps of providing reagents for binding assays of low density or modified low density lipoproteins, adding the compound to be tested, and determining

if the amount of low density or modified low density lipoprotein binding to SR-B1 is altered. The specification provides ample support for this method on pages 43 to 51.

b. Claim 45 meet the written description requirement

Claim 45 is fully supported by the specification and is separately patentable. Claim 45 is drawn to the methods of claim 44 with the further limitation of requiring the assay include expression of the scavenger receptor protein in a cell, where the inhibiting molecule is a nucleic acid which alters expression of the scavenger receptor protein. On page 47, a section entitled, "Generation of nucleic acid regulators" describes methods to design and isolate nucleic acid molecules which inhibit the expression of a variety of proteins, including scavenger receptors.

c. Claim 46 meet the written description requirement

Claim 46 is separately patentable and fully supported by the specification. Claim 46 is drawn to the method of claim 44 wherein the compounds tested are selected from a randomly screened library. This further limitation of the claim is fully supported in the application at page 45:lines 23-40. *In vitro* selection technologies and combinatorial chemistry approaches to the isolation of small molecule inhibitors are well known, and fully applicable to the isolation of molecules that inhibit SR-B1 binding to low density or modified low density lipoprotein.

d. Claim 48 meet the written description requirement

Claim 48 is fully supported by the specification and is separately patentable. Claim 48 is drawn to the screening of patient blood samples and the removal of low density and modified low density lipoprotein from patient blood samples. Support for the elements of this claim can

be found on page 54:lines 9-15. Methods of attaching proteins to solid supports are described and well understood by those of ordinary skill in the art.

e. Claim 49 meet the written description requirement

Claim 49 is fully supported by the specification and is separately patentable. Claim 49 is drawn to a method for inhibiting uptake of lipoprotein or lipids by adipocytes. Support for this claim is found on page 38, lines 1-11 and page 44, lines 3-22. Methods of administration are well understood by those of ordinary skill in the art.

f. Claim 50 meet the written description requirement

Claim 50 is fully supported and separately patentable. Claim 50 is drawn to a method of screening patients to determine if the patients have abnormal levels of SR-B1 receptor or abnormally functioning receptor. The method comprises determining if there is a scavenger receptor present that hybridizes to either SEQ ID NOs. 3 or 7 and binds low density or modified low density lipoprotein, and then determining if the quantity present is similar to normal cells and if the function of the SR-B1 receptor is similar to the SR-B1 receptors of normal cells. There are numerous assays for determining the amount of SR-B1 receptor present in a given cell. For example, from page 32:line 25 to page 33:line 5, methods using antibodies to recognize SR-B1 receptors are described. Those of ordinary skill in the art would readily know how to compare the amounts of SR-B1 protein in control cells to the cells of choice using these type of blotting techniques. The application also describes numerous binding assays to various low density and modified low density lipoproteins that characterizes SR-B1 function. One of

ordinary skill in the art would know how to compare the binding capabilities of the control SR-B1 and the SR-B1 derived from the specific cell or patient being screened.

iii. Rejection of Claims 11-13 , 19-22 and 44-50 under 35 U.S.C. § 112, second paragraph

The Legal Standard

The legal standard for definiteness states that "definiteness of claim language must be analyzed, not in a vacuum, but in light of:

A) The content of the particular application disclosure

B) The teachings of the prior art

C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

In reviewing a claim for compliance with 35 U.S.C. 112, second paragraph, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and therefore, serves the notice function required by 35 U.S.C. 112, second paragraph. See, e.g. Solomon v Kimberly-Clark Corp., 216 F.3d 1372, 1379, 55 USPQ2d 1279, 1283 (Fed.Cir. 2000) (MPEP 2173.02)

The patentable subject matter should be defined with a "reasonable degree of particularity and distinctness". "Some latitude in the manner of expression and the aptness of terms should be permitted even though the claim language is not as precise as the Examiner might desire." (MPEP 2173.02)

Claims 11-13 and 19-22 Meet the Definiteness Requirement

The Examiner's suggestions at page 7 of the Office Action mailed on August 6, 2003, have been noted but are not believed to be necessary. The standard is whether one skilled in the art would know what is defined by the claim. Clearly the examiner fully understands what is meant by the claims, as would others skilled in the art. Attention is drawn to the issued parent, also defining the nucleotide molecules in the same terms, as well as the Acton patent described above (U.S. Patent No. 5,998,141) . Hundreds of other patents have also issued using the language now pending in this application. Accordingly, the claim language meets the requirements of 35 U.S.C. 112, second paragraph, as well as distinguishes the claimed polynucleotides from those encoding CD36.

Scavenger receptor protein type BI and the functions of this protein are described thoughout the specification. Features of scavenger receptor proteins are defined on pages 1-6 in the background of the invention. Binding properties are defined on pages 7 and 11-13 for example. Figures 3, 5, 7, and 8 all describe functions and binding of SR-BI.

The claim element defining hybridization conditions to which a sequence binds is also definite. The claims define a molecule that binds to SEQ ID NO: 3 or SEQ ID NO:7 under moderately stringent conditions. The skilled artisan in molecular biology would readily comprehend what is necessary to obtain moderately stringent hybridization conditions. Salt concentration and temperatures and wash times would all be adjusted appropriately. The conditions are in reference to the probes which in this instance are SEQ ID NO:3 and SEQ ID NO:7 which are two defined nucleotide molecules. One would understand what hybridization

conditions were required to bind to either of these molecules based on knowledge of skill in the art and the defined conditions in the specification that are also included in the claims.

With respect to the issue regarding whether the cDNA encoding SR-BI from two species is adequate to define the cDNA encoding SR-BI from other species, the examiner is referred to the foregoing discussion on enablement, and the previously submitted Declarations under 37 C.F.R. 1.131 and 1.132 (and as referred to, and discussed, above).

Claims 44-50 meet the definiteness requirement

a. Claims 44 and 47 are definite

Claims 44 and 47 are definite and separately patentable. Claims 44 and 47 are drawn to methods for screening for compounds which alter the binding of the low density lipoproteins to the SR-B1 receptor. *These are not drawn to the compounds themselves.* The method comprises the steps of providing reagents for binding assays of low density or modified low density lipoproteins, adding the compound to be tested, and determining if the amount of low density or modified low density lipoprotein binding to SR-B1 is altered. The specification provides ample support for this method on pages 43 to 51 and defines the conditions needed to alter SR-BI binding.

b. Claim 45 is definite

Claim 45 is definite and is separately patentable. Claim 45 is drawn to the methods of claim 44 with the further limitation of requiring the assay include expression of the scavenger receptor protein in a cell, where the inhibiting molecule is a nucleic acid which alters expression of the scavenger receptor protein. On page 47, a section entitled, "Generation of nucleic acid

regulators" describes methods to design and isolate nucleic acid molecules which inhibit the expression of a variety of proteins, including scavenger receptors. These claim elements are definite to one of skill in the art and in few of the teachings of the specification.

c. Claim 46 is definite

Claim 46 is definite and fully supported by the specification. Claim 46 is drawn to the method of claim 44 wherein the compounds tested are selected from a randomly screened library. This further limitation of the claim is fully supported in the application at page 45:lines 23-40. As stated previously, *in vitro* selection technologies and combinatorial chemistry approaches to the isolation of small molecule inhibitors are well known, and fully applicable to the isolation of molecules that inhibit SR-B1 binding to low density or modified low density lipoprotein. The skilled artisan would readily comprehend what is defined by this claim.

d. Claim 48 is definite

Claim 48 is definite and is separately patentable. Claim 48 is drawn to the screening of patient blood samples and the removal of low density and modified low density lipoprotein from patient blood samples. Support for the elements of this claim can be found on page 54:lines 9-15. Methods of attaching proteins to solid supports are described and well understood by those of ordinary skill in the art. The claim elements are defined by the specification and in combination with knowledge in the art.

e. Claim 49 is definite

Claim 49 is definite and is separately patentable . Claim 49 is drawn to a method for inhibiting uptake of lipoprotein or lipids by adipocytes. Support for this claim is found on page

38, lines 1-11 and page 44, lines 3-22. Methods of administration are defined and are well understood by those of ordinary skill in the art.

f. Claim 50 is definite

Claim 50 is definite and separately patentable. Claim 50 is drawn to a method of screening patients to determine if the patients have abnormal levels of SR-B1 receptor or abnormally functioning receptor. The method comprises determining if there is a scavenger receptor present that hybridizes to either SEQ ID NOs. 3 or 7 and binds low density or modified low density lipoprotein, and then determining if the quantity present is similar to normal cells and if the function of the SR-B1 receptor is similar to the SR-B1 receptors of normal cells. There are numerous assays for determining the amount of SR-B1 receptor present in a given cell. For example, from page 32, line 25 to page 33, line 5, methods using antibodies to recognize SR-B1 receptors are described. As stated previously, hybridization techniques are well established in the art. Those of ordinary skill in the art would readily know how to compare the amounts of SR-B1 protein in control cells to the cells of choice using these type of blotting techniques. The application also describes numerous binding assays to various low density and modified low density lipoproteins that characterizes SR-B1 function. One of ordinary skill in the art would know how to compare the binding capabilities of the control SR-B1 and the SR-B1 derived from the specific cell or patient being screened.

(c) Rejections Under 35 U.S.C. § 102

i. Rejection of Claims 11, 13, 19, 20 and 22 under 35 U.S.C. § 102(a) over Calvo et al., J Biol Chem (1993), 268(25): 18929-18935 ("Calvo").

The Legal Standard

For a rejection of claims to be properly founded under 35 U.S.C. § 102, it must be established that a prior art reference discloses each and every element of the claims. *Hybritech Inc v Monoclonal Antibodies Inc*, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 US 947 (1987); *Scripps Clinic & Research Found v Genentech Inc*, 18 USPQ2d 1001 (Fed. Cir. 1991). The Federal Circuit held in *Scripps*, 18 USPQ2d at 1010:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. . . *There must be no difference* between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. (Emphasis added)

A reference that fails to disclose even one limitation will not be found to anticipate, even if the missing limitation could be discoverable through further experimentation. As the Federal Circuit held in *Scripps, Id.*:

> [A] finding of anticipation requires that all aspects of the claimed invention were already described in a single reference: a finding that is not supportable if it is necessary to prove facts beyond those disclosed in the reference in order to meet the claim limitations. The role of extrinsic evidence is to educate the decision-

maker to what the reference meant to persons of ordinary skill in the field of the invention, not to fill in the gaps in the reference.

For a prior art reference to anticipate a claim, it must enable a person skilled in the art to practice the invention. The Federal Circuit held that "a §102(b) reference must sufficiently describe the claimed invention to have placed the public in possession of it. . . [E]ven if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling." *Paperless Accounting Inc v Bay Area Rapid Transit Sys.*, 231 USPQ 649, 653 (Fed. Cir. 1986) (citations omitted).

Legal analysis of 1.131 Declarations

37 C.F.R. § 1.131 states, in pertinent part,

> (a)(1) When any claim of an application . . . is rejected under 35 U.S.C. 102 (a) or (e), or 35 U.S.C. 103 based on . . . reference to . . . a printed publication, the inventor of the subject matter of the rejected claim . . . may submit an appropriate oath or declaration to overcome the . . . publication. The oath or declaration must include facts showing a completion of the invention in this country or in a NAFTA or WTO member country before . . . the date of the printed publication.
>
> * * *

> (b) The showing of facts shall be such, in character and weight, as to establish reduction to practice prior to the effective date of the reference, or conception of the invention prior to the effective date of the reference coupled with due diligence from prior to said date to a subsequent reduction to practice . . . .

The Appellant need only provide evidence that reasonably gives rise to an inference that the invention was completed before the reference date, in order to constitute a *prima facie* showing. No corroboration is required since the application process is *ex parte*. A Rule 131 affidavit is sufficient when it demonstrates that the Appellant has prior "possession" of that part of the invention disclosed by the reference, as is the case when a reference discloses a species falling within a claim to its genus. *See* Donald S. Chisum, **Patents** § 3.08[1][b] (Matthew Bender & Co. 1996). Possession in this context is shown by demonstrating conception, reduction to practice, and diligence--each as normally required in determining the date of invention. *See In re Mulder*, 716 F.2d 1542 (Fed. Cir. 1983).

In *In re Stempel*, 241 F.2d 755 (C.C.P.A. 1957), the court held that Appellant's affidavit under Rule 131 was not required to show priority with respect to the claimed genus, but only to the species disclosed by the cited reference, in order to remove that reference as prior art. The claims, both genus and species were drawn to chemical compounds. *Stempel* overcame the anticipation rejection by showing reduction to practice, prior to the effective date of the reference, of a species of the invention within the generic claims.

In *In re Tanczyn,* 347 F.2d 830 (C.C.P.A. 1965), the court qualified *In re Stempel*, stating that the *Stempel* doctrine did not apply to *partial* possession of the invention, as distinguished from *total* possession of a species within a genus claim. The *Tanczyn* application "did not involve a genus-species relationship." Id. at 833.

In *In re Clarke,* 356 F.2d 987 (C.C.P.A. 1966), the court extended the *Stempel* doctrine to the situation more at issue in this application, that is, where the Appellant's Rule 131 affidavit shows possession of representative species of the claimed genus, not of the specific species disclosed by the reference. The *Clarke* court held that the affidavit is sufficient to remove a reference where the Appellant demonstrates possession of such "invention" as to make the entire claimed invention or the reference part obvious to one of ordinary skill in the art. The court stated,

> "[i]n an appropriate case an Appellant should not be prevented from obtaining a patent to an invention where a compound described in a reference would have been obvious to one of ordinary skill in the art in view of what the affiant proves was completed with respect to the invention prior to the effective date of the reference. . . . Thus, we think that in an appropriate case a single species could be sufficient to antedate indirectly a different species of a reference.".

The CCPA also has phrased the rule, "[w]hen that species of the generic invention which has been completed prior to the effective date of the reference would make obvious to one of

ordinary skill in the art the species disclosed in the reference, the reference may be said to have been 'indirectly antedated.'" *In re Schaub*, 537 F.2d 509, 512 (C.C.P.A. 1976) (quoting *In re Ranier*, 390 F.2d 771, 773-74 (C.C.P.A. 1968)). The *Schaub* court stated that "[a]ppellants have made a *prima facie* case that the compound of the reference is obvious from the compounds which they have made prior to the date of the reference. Appellants' compound III is the next higher homolog of the reference compound II, . . ." Id. at 512-13.

There is little, if any, Federal Circuit case law on point. However, the rule established in *In re Clarke* apparently remains valid, as one somewhat recent, "unpublished" (i.e. not citable as precedent) case seems to indicate. In *In re Rozmus*, 928 F.2d 412, 1991 WL 17232 (Fed. Cir.), the court stated that "[a]lthough Rozmus' [Rule 131] declaration showed reduction to practice of only a species of the generic invention, that alone is not fatal to his claim. A declaration proving a species is also sufficient to show possession of 'variations and adaptations which would, at the same time, be obvious to one skilled in the art.'" (quoting *In re Spiller*, 500 F.2d 1170, 1178 n.5 (CCPA 1974)).

Other cases discussing priority but which do not involve Rule 131 have stated, "[p]riority as to a genus may . . . be shown by prior invention of a single species, but the genus will not be patentable to an Appellant unless he has generic support therefor." *In re Zletz*, 893 F.2d 319, 323 (Fed. Cir. 1989); *see also Hoffman v. Schoenwald* 15 U.S.P.Q.2d 1512, 1514 (Bd. Pat. App. & Int'f 1990) ("Conception of a species within the genus constitutes conception of the genus for priority of invention purposes.").

Claims 11, 13, 19, 20 and 22 are Novel

Appellants have clearly demonstrated conception and reduction to practice of the claimed genus prior to Calvo. Therefore Calvo should not be available as prior art to claims 11, 13, 20 and 22. The only claim in issue is claim 19, drawn to the DNA encoding the human SR-BI protein.

Calvo, et al. reported isolation of a cDNA encoding a member of the CD36 superfamily. The protein was not physically isolated nor was the cloned DNA expressed, much less expressed on the surface of cells and shown to be functional, although a small piece non-functional portion (the carboxyl terminal region including residues 365-409) was expressed as a chimeric protein (page 18930). The function of the protein was not known, although its resemblance to CD36/LimpII was recognized based on the predicted similarities in structure and the authors speculated that "on the basis of its structural homology to CD36 that CLA-1 could act as a receptor for extracellular products" (page 18934).

As demonstrated repeatedly by Appellants and discussed above, CD36 and SR-BI are *not* the same proteins nor do they have the same binding activity.

A Declaration under 37 C.F.R. §1.131, submitted in the parent application, U.S. Serial No. 08/265,428, filed June 23, 1994, which demonstrates that a cDNA and encoded protein defined by the claims in issue was conceived and reduced to practice prior to the publication of Calvo, et al. was submitted with the Response to An Office Action, mailed on December 29, 1997. Appellants cloned the gene, they expressed the protein, and they characterized the protein and showed its function, **prior to** Calvo's publication date.

The Examiner has stated that the Declaration under Rule 1.131 does not "demonstrate that the Appellants was in possession of the any information regarding a CLA-1 protein or CLA-1 gene from any animal other than hamster prior to the publication of Calvo et al." Appellants respectfully point out that this is not in fact true. Submitted with the Declaration is a printout obtained from the search of six databases (PDP, Swissprot, PIR, SPupdate, Genpept, GPupdate). This printout indicates that the Rat LimpII gene and the CD36 gene were among the genes with the highest homology to SR-B1. While these genes have been shown to be members of a different families within the superfamily of CD36 scavenger receptors than the SR-B1 proteins of the present application, for one of ordinary skill in the art they presented a nexus between the species described in the Declaration of Krieger and Acton and the genus which would include the CLA-1 gene described in Calvo et al. The validity of these assertions is evidenced by the fact that the CLA-1 gene was isolated using primers derived from CD-36 and LIMP II, related but non-homologous proteins. Surely, the possession of the homolog of the CLA-1 protein, with the information that it fell within the CD-36 superfamily, is more information than Calvo et al. had when they cloned the CLA-1 gene, but not the homolog, from rat. The Appellants clearly were in possession of the genus of SR-B1 proteins and nucleic acid molecules that encode these proteins prior to the publication of Calvo.

Furthermore, the Examiner has stated, "There is no evidence in this Declaration that a nucleic acid probe encoding all or part of hamster CLA-1 was capable of hybridizing to mouse DNA or that a DNA encoding a murine cDNA had been isolated." This statement is incorrect. The latter is obviously wrong - SEQ ID NO. 7 *is* the nucleic acid sequence encoding the murine

SR-BI. Moreover, the specification provides exactly the type of evidence the Examiner is looking for. For example, on page 18:line 27 to page 19:line 6 there is an explicit description of a hybridization procedure in which a 600 base probe of derived from the hamster SR-B1 cDNA is used to probe different cell types from murine tissues and from 3T3 cells. The results from these experiments clearly shows that a single predominant band of 2.4 kb was abundant in fat and present in moderate levels in lung and liver (page 31:line 11 to page 32:line 24). This data not only directly indicates an interspecies hybridization abundance, it indicates that this relationship is specific and successful because it recognizes the murine homologue in only those tissues that express it. The genus of the claims is described as cDNAs encoding Scavenger Receptor Protein type B1, having specific functional properties, and includes the SR-B1 cDNA of the present application and the CLA-1 cDNA of Calvo et al. This genus is a subgenus of the genus of CD36 superfamily of scavenger receptor proteins which includes CD36 and LimpII.

To one of ordinary skill in the art there would have been more than sufficient motivation given the sequence homology data presented in the Declaration to utilize the information obtained from the novel hamster SR-B1 to isolate the human homologue based on the information provided in the specification and the general knowledge known in the art. The claimed sequence would have been obvious due to the high degree of homology and sequence identity, the exact same protein structure and function, and the ready available of reagents and methods enabling the isolation of the nucleotide molecule.

The claimed sequences are novel because Calvo et al. has been antedated by the Krieger and Acton Rule 1.131 Declaration. Furthermore, the nature of the art is such that upon obtaining

the sequences of the haSR-B1 and the murine SR-B1 those of ordinary skill in the art would have found it obvious to obtain the homologs to these nucleic acid molecules for the reasons outlined above.

The declaration also establishes prior conception of the genus and representative species, followed by diligent reduction to practice of the human species.

Calvo et al. does not disclose, nor has Calvo et al. been alledged to disclose, the expression of the proteins encoded by the nucleic acid molecules described in claim 11 in adipocyte, lung, or liver cells. As discussed above, these limitations are fully enabled in the present application and render the claims novel over Calvo et al.

Claim 19 is novel and separately patentable over Calvo et al. because as discussed above the Rule 1.131 Declaration presented by Drs. Krieger and Acton prove that the Appellants were in possession of the claimed subject matter prior to the publication of Calvo et al. Furthermore, as discussed above, the inventive efforts of the Appellants made obvious the cloning of other SR-B1 homologs and therefore, the 1.131 Declaration is sufficient to antedate a "different species" within the genus.

(d) Rejections Under 35 U.S.C. § 103

i. Rejection of Claim 21 under 35 U.S.C. § 103(a) over Calvo et al., J Biol Chem (1993), 268(25): 18929-18935 ("Calvo").

The Legal Standard

The law is quite clear that, for the Patent Office to establish a *prima facie* case of obviousness of claimed subject matter, the prior art references relied upon must provide *both* a

suggestion to make the claimed invention and a reasonable expectation of success. It is also clear that the whole field of the invention must be considered, including those publications which teach away from the claimed invention. Particularly relevant to the matters under consideration here are the decisions of the Court of Appeals for the Federal Circuit in *In re Dow Chemical*, 5 USPQ2d 1529 (1988) and *In re Vaeck*, 20 USPQ2d 1438 (1991). The *Dow* Court noted that:

> The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in light of the prior art.... Both the suggestion and expectation of success must be founded in the prior art, not in the Appellant's disclosure.
>
> In determining whether such a suggestion can fairly be gleaned from the prior art, *the full field of the invention must be considered*: for the person of ordinary skill is charged with knowledge of the entire body of technological literature, including that which might lead away from the claimed invention.... Evidence that supports, rather than negates, patentability must be fairly considered.

5 USPQ 2d at 1531-1532 (Citations omitted, emphasis added).

In *In re Dow Chemical*, a combination of three components forming an impact resistant rubber-based resin was not found to be obvious based upon art disclosing the individual components. The court noted that the record had shown that the claimed combination had

previously been made, *but did not produce the product desired.* "That there were other attempts, and various combinations and procedures tried in the past, does not render obvious the later successful one.... Recognition of need, and difficulties encountered by those skilled in the field, are classical indicia of unobviousness," *Id.* at 1531 (citations omitted). The Court found that none of the prior art cited by the Appellant and the PTO suggested that any process could be used successfully in this three-component system to produce the product having the desired properties. Further, the Court stated that evidence from an expert expressing skepticism as to the success of the claimed combination before these inventors proved him wrong should be considered. *Id.* at 1532.

Claims 21 is not obvious in view of Calvo et al.

The Board stated in their decision at page 13 "we remind the examiner, if the prior art does not teach any specific or significant utility for the disclosed compounds, then the prior art is not sufficient to render structurally similar claims *prima facie* obvious because there is no motivation for one of ordinary skill in the art to make the reference compounds, much less any structurally related compounds. *In re Stemniski*, 444 F.2d 581, 586, 170 USPQ 343, 348 (CCPA 1971).

As discussed above, the Krieger and Acton Declaration clearly shows that the Appellants were in possession of the cDNA and expressed protein prior to the date of Calvo et al. Therefore, Calvo et al. is antedated and not effective as 35 U.S.C. § 103 art.

However, even it if were available as prior art, it cannot make obvious the genus where there was no expression of a protein, nor recognition of its properties.

Among the reasons that the Examiner has argued that it would be obvious to go from the Human CLA-1 gene described by Calvo et al. to the hamster homologue are: (1) CLA is described as being structurally analogous to LIMPII: (2) amino acid sequence were highly conserved between human and rat LIMPII; (3) the genes had sufficient similarity to permit the isolation of LIMPII; (4) an artisan would have concluded that any mammalian protein encoding CLA-1 would have been readily isolated by probing a DNA library, since the hamster, as well as rat, was routinely employed as a laboratory model for determining the physiological significance of proteins of human origin since the scope of human experimentation is obviously limited, (5) and there was knowledge that there was homology between humans and rodents at the time. [Appellants note, in passing, that each and every one of these reasons, relied upon by the Examiner to support the "*prima facie*" case of obviousness to clone the hamster SR-B1 protein from the sequence information of the human CLA-1 protein were presented in the specification and Declaration in the present application, and one must assume that the Examiner may have used hindsight based on this Declaration to identify reasons why one would go from Calvo to what is claimed, rather than from what Appellants have demonstrated they conceived and reduced to practice, prior to Calvo, to arrive at what Calvo disclosed.]

Appellants do not understand how, in the light of the Declaration submitted, the Examiner can maintain that it was *prima facie* obvious to clone the hamster homologue of the human CLA-1 when Appellants have demonstrated possession of the hamster gene before the date of the publication of the human homologue CLA-1. Furthermore, in light of the Examiner's rejection of claim 19 under 35 U.S.C § 112 for an inadequate description of the human

homologue of SR-B1, which implicitly relies on *Regents of the University of California v. Eli Lilly and Company*, 43 USPQ2d. 1398 (CAFC 1997), it is inconsistent to maintain a rejection which is contrary to the Examiner's only interpretation and reliance on case law. Appellants have distinguished themselves not only from *Regents of the University of Californiā v. Eli Lilly and Company* (as discussed above), but also assert that in the light of the Declaration and the evidence provided in the specification, it would have been *prima facie* obvious to clone the human homologue of SR-B1 from what Appellants had well prior to the publication by Calvo!

Appellants have demonstrated that they cloned and expressed the hamster gene encoding the claimed SR-BI proteins, and that the gene hybridizes to the murine gene, prior to publication by Calvo et al. Accordingly, Appellants conceived of and reduced to practice the claimed invention prior to Calvo et al. Therefore, the Declaration under 37 C.F.R. §1.131 should conclusively remove Calvo et al. as a reference, and the claims found patentable to Appellants.

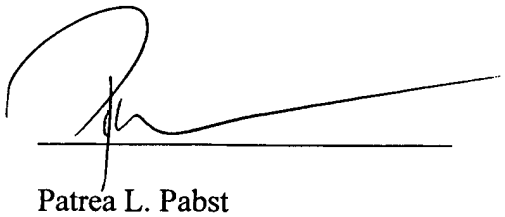
Claim 21 is not made obvious by Calvo et al. Calvo et al. does not disclose the expression of the molecules of claim 11 in either adipocytes, lung cells, or liver cells, nor for that matter, in any cell type. The Examiner has failed to meet his burden of establishing a *prima facie* case of obviousness because there has been no showing that Calvo et al. ever expressed active, functional protein, knew what function to look for, or how to look for related proteins. In addition, there is nothing in Calvo et al. that would lead one to express the molecules of claim 11 in adipocyte, lung, or liver cells. Therefore, claim 21 is patentable over Calvo et al.

(9) SUMMARY AND CONCLUSION

In conclusion, claims 11-13, 19-22 and 14-50 are enabled under 35 U.S.C. § 112, first paragraph, because the limitation of hybridization and specific lipoprotein binding limit the claims and appellants have provided evidence that other variants and homologues from other species could be obtained using only routine methodology. The declaration by Dr. Krieger and Dr. Acton support the enablement of the disclosure in view of the knowledge in the art at the time of filing. Claims 11-13, 19-22 and 44-50 are not vague and indefinite under 35 U.S.C. §112, second paragraph. Claims 11, 12, 15, 19 and 20 are novel under 35 U.S.C. § 102(a) over Calvo *et al. J Biol Chem (1993), 268(25): 18929-18935 ("Calvo")* and claim 21 is not obvious under U.S.C. § 103 over Calvo *et al. J Biol Chem (1993), 268(25): 18929-18935 ("Calvo")* because the Rule 1.131 Declaration presented by Drs. Krieger and Acton show that the Appellants were in possession of the claimed subject matter prior to the publication of Calvo *et al.*

For the foregoing reasons, Appellant submits that the claims 11-13, 19-22, and 44-50 are patentable.

Respectfully submitted,



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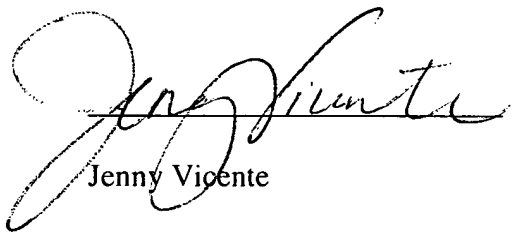

Jenny Vicente

Date: February 6, 2004

Appendix: Claims On Appeal

1-10. (cancelled)

11. (previously presented) An isolated nucleic acid molecule encoding a functional scavenger receptor protein type BI which selectively binds to low density lipoprotein and to modified lipoprotein having the characteristics of acetylated low density lipoprotein in cell medium containing 10% serum, which hybridizes to SEQ ID Nos. 3 and 7 under moderately stringent hybridization conditions at a temperature of approximately 25°C below the melting temperature of a perfectly base-paired double-stranded DNA.

12. (previously presented) The molecule of claim 11 expressed in cells selected from the group consisting of adipocytes, lung cells and liver cells.

13. (previously presented) The molecule of claim 11 hybridizing under stringent hybridization conditions at a temperature greater than 25°C below the melting temperature of a perfectly base-paired double-stranded DNA to a molecule with Sequence ID No. 3.

14. (previously presented) An isolated nucleic acid molecule encoding a scavenger receptor protein having the sequence of Sequence ID No. 3.

15. (previously presented) An isolated nucleic acid molecule encoding a protein with the amino acid sequence shown in Sequence ID No. 4.

16-18. (canceled)

19. (previously presented) The molecule of claim 11 which encodes a human scavenger receptor.

20. (previously presented) The molecule of claim 11 labeled with a detectable label.

21. (previously presented) An expression vector comprising the molecule of claim 11 encoding the scavenger receptor protein.

22. (previously presented) A host cell comprising the nucleic acid molecule of claim 11.

23-43. (cancelled)

44. (previously presented) A method for screening for a compound which alters the binding of scavenger receptor protein type BI, which is encoded by a nucleotide molecule hybridizing to SEQ ID Nos. 3 and 7 under moderately stringent hybridization conditions at a temperature of approximately 25°C below the melting temperature of a perfectly base-paired double-stranded DNA and which selectively binds to low density lipoprotein and to modified lipoprotein having the characteristics of acetylated low density lipoprotein in cell medium containing 10% serum, comprising

providing reagents for use in an assay for binding of low density lipoprotein or modified low density lipoprotein to the scavenger receptor protein the reagents comprising SR-BI, low density lipoprotein or modified low density lipoprotein, and means for determining if the low density lipoprotein or modified low density lipoprotein is bound to the scavenger receptor protein,

adding the compound to be tested to the assay, and

determining if the amount of modified low density lipoprotein or low density lipoprotein which is bound to the scavenger receptor protein is altered as compared to binding in the absence of the compound to be tested.

45. (previously presented) The method of claim 44 wherein the assay includes a cell expressing the scavenger receptor protein and the compound is a nucleic acid molecule which alters expression of the scavenger receptor protein.

46. (previously presented) The method of claim 44 wherein the compound is selected from a library of compounds which are randomly tested for alteration of binding.

47. (previously presented) The method of claim 44 wherein the compound competitively inhibits binding of low density lipoprotein or modified lipoprotein having the characteristics of acetylated low density lipoprotein to the scavenger receptor protein.

48. (previously presented) A method for removing low density lipoprotein from patient blood comprising reacting the blood with immobilized scavenger receptor protein type B, wherein the scavenger receptor protein type BI is encoded by a nucleotide molecule hybridizing to SEQ ID Nos. 3 and 7 under moderately stringent hybridization conditions at a temperature of approximately 25°C below the melting temperature of a perfectly base-paired double-stranded DNA and selectively binds to low density lipoprotein and to modified lipoprotein having the characteristics of acetylated low density lipoprotein in cell medium containing 10% serum, under conditions wherein the low density lipoprotein is bound to the scavenger receptor.

49. (previously presented) A method for inhibiting uptake of lipoprotein or lipids by adipocytes comprising

administering a compound selectively inhibiting binding of lipoprotein to the scavenger receptor protein type BI, wherein the scavenger receptor protein type BI is encoded by a nucleotide molecule hybridizing to SEQ ID Nos. 3 and 7 and selectively binds to low density

lipoprotein and to modified lipoprotein having the characteristics of acetylated low density lipoprotein, under conditions wherein the low density lipoprotein is bound to the scavenger receptor.

50. (previously presented) A method for screening patients for abnormal scavenger receptor protein activity or function comprising

determining the presence of scavenger receptor protein type BI, wherein the scavenger receptor protein type BI is encoded by a nucleotide molecule hybridizing to SEQ ID Nos. 3 and 7 under moderately stringent hybridization conditions at a temperature of approximately 25°C below the melting temperature of a perfectly base-paired double-stranded DNA and selectively binds to low density lipoprotein and to modified lipoprotein having the characteristics of acetylated low density lipoprotein, and

determining if the quantity present or the function of the receptor is equivalent to that present in normal cells.

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(d) Rejections Under 35 U.S.C. § 103

i. Rejection of Claim 21 under 35 U.S.C. § 103(a) over Calvo et al., J Biol Chem (1993), 268(25): 18929-18935 ("Calvo").

(9) SUMMARY AND CONCLUSION

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Appendix: Claims On Appeal

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